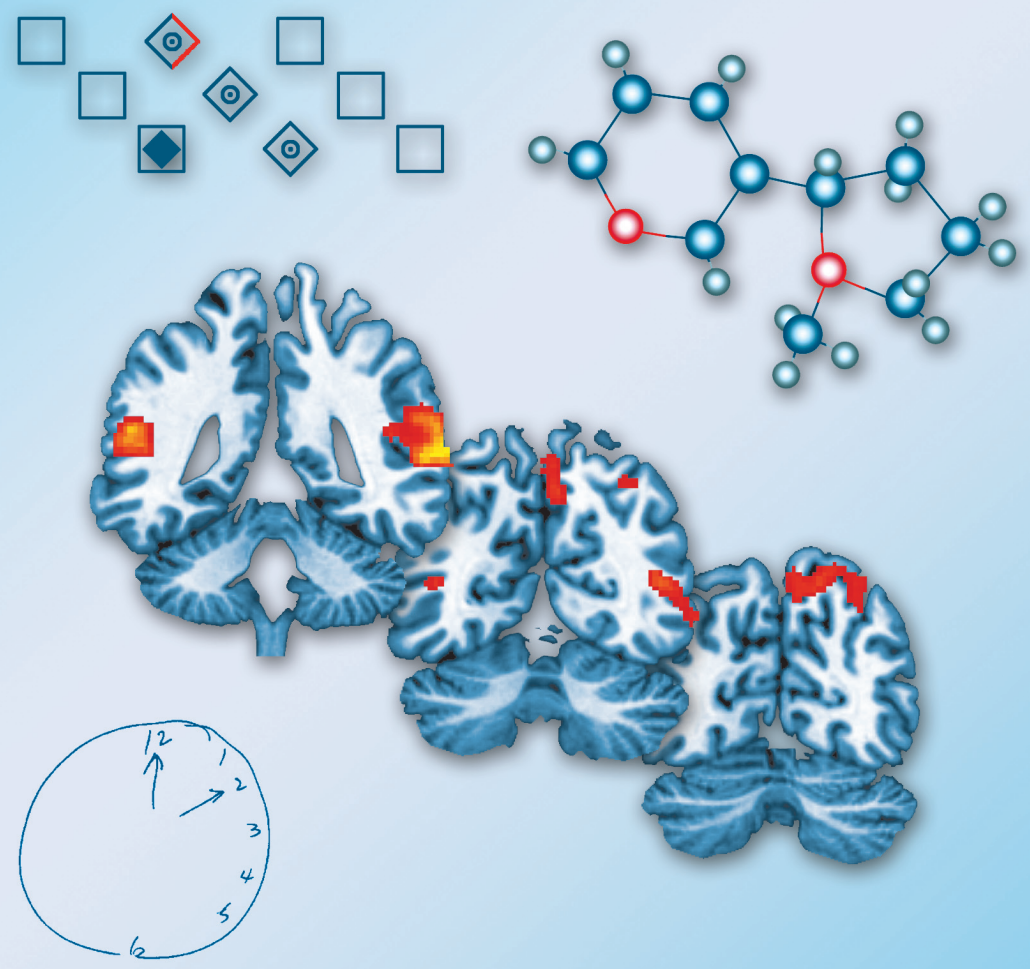

Visuospatial Attention: Neural Correlates and Pharmacological Modulation in Healthy Subjects and Patients with Spatial Neglect

Simone Vossel

JÜLICH
FORSCHUNGSZENTRUM

Mitglied der Helmholtz-Gemeinschaft

Schriften des Forschungszentrums Jülich
Reihe Gesundheit / Health Band / Volume 7

Forschungszentrum Jülich GmbH
Institut für Neurowissenschaften und Biophysik (INB)
Medizin (INB-3) – Kognitive Neurologie

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ISSN 1866-1785 ISBN 978-3-89336-526-5

Bibliographic information published by the Deutsche Nationalbibliothek.
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available in the Internet at http://dnb.d-nb.de.

Publisher and Distributor:	Forschungszentrum Jülich GmbH Zentralbibliothek, Verlag D-52425 Jülich phone: +49 2461 61-5368 · fax:+49 2461 61-6103 e-mail: zb-publikation@fz-juelich.de Internet: http://www.fz-juelich.de/zb
Cover Design:	Grafische Medien, Forschungszentrum Jülich GmbH
Printer:	Grafische Medien, Forschungszentrum Jülich GmbH
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Schriften des Forschungszentrums Jülich
Reihe Gesundheit / Health Band / Volume 7

D 45 (Diss., Oldenburg, Univ., 2008)

ISSN 1866-1785
ISBN 978-3-89336-526-5

The complete volume is freely available on the Internet on the Jülicher Open Access Server (JUWEL) at http://www.fz-juelich.de/zb/juwel

“The question is not what you look at, but what you see.”

- Henry D. Thoreau

Preface

The present thesis was conducted at the Institute of Neuroscience and Biophysics – Medicine at the Research Centre Jülich. The work deals with the neural and neurochemical systems in the brain mediating reorienting processes of visuospatial attention. Three experiments were done to investigate the neural correlates of reorienting of attention as well as the cholinergic modulation of attentional reorienting in healthy subjects and neurological patients with spatial neglect.

I thank all colleagues of the Institute of Neuroscience and Biophysics – Medicine as well as all volunteers and patients that contributed to this thesis. In particular, I want to thank my supervisor Professor Christiane Thiel for all the things I could learn from her and for her ceaseless commitment and interest in the present work. I am also very grateful to Professor Gereon Fink for all his valuable support and for giving me the opportunity to accomplish this work in the first place. Moreover, I wish to thank Sarah Brieber, Carsten Giessing, Juraj Kukolja, Verena Vorhold, Ralph Weidner and Peter Weiss-Blankenhorn for their professional as well as their social support.

Finally, my deepest gratitude goes to my parents for making all this possible.

Jülich, March 2008

Simone Vossel

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Abbreviations

ACh	acetylcholine
ang	angular gyrus
ANOVA	analysis of variance
ASL	arterial spin labeling
BOLD	blood oxygen level dependent
CBF	cerebral blood flow
EPI	echoplanar image
FDR	false discovery rate
FEF	frontal eye fields
fMRI	functional magnetic resonance imaging
fMRT	funktionelle Magnet-Resonanz-Tomographie
FWHM	full-width half-maximum
GLM	general linear model
HPLC	high performance liquid chromatography
H	hemianopia
HRF	haemodynamic response function
Hz	Hertz
IFG	inferior frontal gyrus
IPS	intraparietal sulcus
IPL	inferior parietal lobe
IQ	inferior quadrantanopia
MFG	middle frontal gyrus
ml	millilitre
mm	millimetre
MNI	Montreal Neurological Institute
MRI	magnetic resonance imaging
ms	milliseconds
NET	Neglect-Test

ng	nanogramme
OTC	occipito-temporal cortex
PET	positron emission tomography
PFC	prefrontal cortex
ReML	restricted maximum likelihood
RF	radiofrequency
ROI	region of interest
RT	reaction time
rTMS	repetitive transcranial magnetic stimulation
s	second
SEM	standard error of the mean
SD	standard deviation
smg	supramarginal gyrus
SOA	stimulus onset asynchrony
SPL	superior parietal lobe
SPM	statistic parametric mapping
SQ	superior quadrantanopia
STG	superior temporal gyrus
T	Tesla
TAP	Testbatterie zur Aufmerksamkeitsprüfung
TPJ	temporo-parietal junction
VFC	ventral frontal cortex
VSTM	visual short term memory

0. Summary

The detection of relevant stimuli occurring outside of the current focus of attention is an essential cognitive ability of both animals and humans. The present thesis concentrates on the neural and neurochemical mechanisms in the human brain that underlie the processing of unattended stimuli requiring reorienting of visuospatial attention. To study these processes, Posner's location-cueing paradigm (Posner, 1980) was employed. Here, spatial cues predict the location of a behaviourally relevant target stimulus with a certain probability and the difference in reaction times between invalidly and validly cued targets (termed the 'validity effect') is taken as an indicator for the speed of reorienting of attention. Functional magnetic resonance imaging (fMRI) in combination with psychopharmacology was used to investigate the reorienting-related neural systems in the brain.

This thesis is concerned with the question how the neural processes of attentional reorienting are modulated by cognitive as well as by pharmacological factors. Prior studies have shown that attentional reorienting is one cognitive function that can be modulated pharmacologically by cholinergic agents. In the location-cueing paradigm the administration of the cholinergic agonist nicotine leads to faster reaction times to invalidly cued targets and consequently to a decreased validity effect (e.g., Witte, Davidson & Marrocco, 1997). This behavioural effect is accompanied by a reduction of reorienting-related neural activity in the parietal cortex (Thiel, Zilles & Fink, 2005). Drug-induced changes in the processing of the probabilistic top-down information of the spatial cues about the target location have been proposed to underlie this pharmacological effect (Yu & Dayan, 2005).

Thus, a first aim of the present thesis was to study how reorienting towards unattended events can be manipulated by the top-down information about their location (i.e., by cue validity) and how the effects of this cognitive modulation are represented in the brain in a placebo condition. It was observed that the effects of a cue validity manipulation resembled the effect of nicotine in the location-cueing paradigm, since low cue validity (60%) decreased the validity effect as well as reorienting-related neural activity in right frontal and parietal cortex when compared to a high cue validity condition (90%).

A further aim of the thesis was to examine the interaction effects between the cognitive and the pharmacological modulation of attentional reorienting at the behavioural as well as the neural level. Given that nicotine is supposed to reduce the

use of top-down information, it was expected that the pharmacological effect should rather be observed in the high than in the low cue validity condition. In line with this hypothesis, nicotine reduced the validity effect in the 90% but not in the 60% cue validity condition. Similarly, the reduction of neural activity in right frontal and parietal brain areas was more pronounced in the high than in the low cue validity condition.

The second experiment of the thesis aimed at a closer investigation of the functions of those brain regions involved in spatial attentional reorienting as identified with Posner's location-cueing paradigm. In the location-cueing paradigm, invalid trials are presented with a lower frequency than valid trials and thus differ with regard to the unexpectedness and saliency. This difference varies as a function of the validity of the cue which is determined by the ratio between invalidly and validly cued targets. Thus, following up the results of the first experiment, it was tested in a second fMRI study without pharmacological challenge whether the regions activated by invalidly more than by validly cued targets are generally involved in the detection of rare and unexpected stimuli. In other words, it was attempted to dissociate the neural correlates of spatial reorienting of attention from the brain response to infrequently occurring deviant stimuli (colour and orientation changes of the target stimulus) per se. Right superior parietal activation and bilateral activation of the temporo-parietal junction was observed when contrasting invalid and valid trials but not when comparing deviant and standard targets. In contrast, bilateral occipito-temporal, left inferior parietal and right frontal areas were more activated by deviant than by standard targets. The only common activation was observed in an area near the right intraparietal sulcus and in the right inferior frontal gyrus. Thus, the brain response to invalidly cued targets was shown to be different to the response to non-spatial deviant targets.

In the third study of the thesis, it was tested whether a cholinergic stimulation via nicotine can be used as a clinical application to ameliorate the attentional reorienting deficit in neurological patients with chronic spatial neglect. After right-hemispheric brain damage a considerable proportion of patients shows neglect of the left side of space in that responses to left events and the exploration of left space are impaired. This spatial bias manifests itself also in the location-cueing paradigm since here in particular reaction times to invalidly cued left-sided target stimuli are disproportionately slow in many neglect patients. Since it was observed in experiment 1 that nicotine can speed up attentional reorienting when the validity effect is high, it was expected that the validity effect for left targets would be reduced by nicotine in neglect patients. This pharmacological effect was observed in a subsample of patients and depended on the lesion site.

0. Zusammenfassung

Relevante Reize zu entdecken - auch wenn sie außerhalb des aktuellen Aufmerksamkeitsfokus auftreten - ist eine grundlegende kognitive Fähigkeit von Tier und Mensch. Die vorliegende Arbeit beschäftigt sich mit den neuronalen und neurochemischen Mechanismen im menschlichen Gehirn, die der Reorientierung visuell-räumlicher Aufmerksamkeit auf zuvor unbeachtete Reize zugrunde liegen. Um diese Prozesse experimentell zu untersuchen, wurde das Hinweisreizparadigma von Posner (1980) verwendet. In diesem Paradigma sagen räumliche Hinweisreize den Auftretensort eines reaktionsrelevanten Zielreizes mit einer bestimmten Wahrscheinlichkeit voraus. Die Differenz in den Reaktionszeiten auf invalide und valide angezeigte Zielreize (der sog. ‚Validitätseffekt') wird hierbei als Indikator für die Geschwindigkeit der Aufmerksamkeitsreorientierung herangezogen. In der vorliegenden Arbeit wurde das bildgebende Verfahren der funktionellen Magnet-Resonanz-Tomographie (fMRT) angewendet und mit psychopharmakologischen Methoden kombiniert, um diejenigen neuralen Systeme im Gehirn zu untersuchen, die der Reorientierung der Aufmerksamkeit zugrunde liegen.

Die Arbeit konzentriert sich auf die Frage, wie Reorientierungsprozesse der Aufmerksamkeit durch kognitive wie auch pharmakologische Faktoren moduliert werden. Frühere Studien haben gezeigt, dass die Reorientierung visuell-räumlicher Aufmerksamkeit eine kognitive Funktion ist, die pharmakologisch durch Substanzen, die auf das cholinerge Neurotransmittersystem im Gehirn einwirken, moduliert werden kann. In dem Hinweisreizparadigma führt die Gabe von cholinergen Agonisten, wie z.B. Nikotin, zu schnelleren Reaktionszeiten in invaliden Durchgängen und somit zu einer Verringerung des Validitätseffektes (z.B. Witte, Davidson & Marrocco, 1997). Mit diesem Verhaltenseffekt geht eine Verringerung neuronaler Aktivität im Parietalcortex einher (Thiel, Zilles & Fink, 2005). Es wird angenommen, dass pharmakologisch induzierte Änderungen in der Verarbeitung der ‚top-down'-Information der Hinweisreize über den Auftretensort des Zielreizes diesem Effekt zugrunde liegen (Yu & Dayan, 2005).

Ein erstes Ziel der Arbeit war somit zu untersuchen, wie die Reorientierung der Aufmerksamkeit durch ‚top-down'-Information über den Auftretensort dieser Reize (d.h., durch die Hinweisreizvalidität) manipuliert werden kann und wie sich diese kognitive Modulation in der Gehirnaktivierung in einer Placebo-Bedingung widerspiegelt. Es wurde beobachtet, dass der Effekt einer Manipulation der Hinweisreizvalidität dem Effekt von Nikotin im Hinweisreizparadigma ähnelt, da -

verglichen mit hoher Hinweisreizvalidität (90%) - geringe Hinweisreizvalidität (60%) zu einer Verringerung des Validitätseffektes und der Aktivierung in frontalen und parietalen Hirnregionen der rechten Hemisphäre führten.

Ein weiteres Ziel dieser Arbeit war es, Interaktionseffekte zwischen der kognitiven und der pharmakologischen Modulation der Aufmerksamkeitsreorientierung auf der Verhaltens- wie auch der neuronalen Ebene zu untersuchen. Ausgehend von der Annahme, dass Nikotin den Einfluss der ‚top-down'-Information der Hinweisreize verringert, wurde erwartet, dass der pharmakologische Effekt eher bei hoher als bei niedriger Hinweisreizvalidität auftreten wird. In Übereinstimmung mit dieser Hypothese konnte gezeigt werden, dass Nikotin den Validitätseffekt in der 90%-, nicht aber in der 60%- Bedingung verringerte. Ebenso war die Reduktion neuronaler Aktivität in rechtshemisphärischen frontalen und parietalen Hirnregionen bei hoher Hinweisreizvalidität stärker als bei niedriger Hinweisreizvalidität.

Das zweite Experiment der vorliegenden Arbeit zielte darauf ab, die Funktionen derjenigen Hirnareale näher zu untersuchen, die der räumlichen Aufmerksamkeitsreorientierung im Hinweisreizparadigma zugrunde liegen. Da in diesem Paradigma die invaliden Durchgänge seltener dargeboten werden als die validen, unterscheiden sich die beiden Bedingungen auch im Grad der Unerwartetheit und Salienz. Dieser Unterschied variiert als Funktion der Hinweisreizvalidität, die durch das Verhältnis von validen und invaliden Durchgängen determiniert ist. Anknüpfend an die Ergebnisse des ersten Experiments wurde somit in einer zweiten fMRT-Studie ohne pharmakologische Beeinflussung untersucht, ob die Hirnregionen, die in invaliden Durchgängen stärkere Aktivierung zeigen als in validen, generell an der Detektion selten auftretender unerwarteter Reize beteiligt sind. Es wurde somit angestrebt, die neuronalen Korrelate räumlicher Aufmerksamkeitsreorientierung von der Hirnaktivierung bei der Verarbeitung selten auftretender abweichender Reize (Farb- und Orientierungsänderungen der Zielreize) zu dissoziieren. Bei der Kontrastierung invalide und valide angezeigter Zielreize wurde rechtshemisphärische superior parietale Aktivierung und bilaterale Aktivierungen des temporo-parietalen Cortex beobachtet. Dagegen wurden bilaterale occipito-temporale, linkshemisphärisch inferior parietale und rechtshemisphärisch frontale Areale stärker durch die seltenen Reizänderungen aktiviert als durch die Standardzielreize. Damit konnte gezeigt werden, dass sich die Antwort des Gehirns auf invalide angezeigte Zielreize von der unterscheidet, die bei Änderungen in nicht-räumlichen Reizeigenschaften auftritt.

Im dritten Experiment der Arbeit sollte geprüft werden, ob die Verabreichung des cholinergen Agonisten Nikotin das Reorientierungsdefizit von neurologischen Patienten mit chronischem räumlichem Neglekt verbessern kann. Insbesondere nach rechtshemisphärischer Hirnschädigung zeigt ein großer Anteil der Patienten einen Neglekt für die linke Raumhälfte, so dass ihre Reaktionen auf Ereignisse sowie ihre Exploration des linksseitigen Raums beeinträchtigt sind. Dieses räumliche Defizit wird auch im Hinweisreizparadigma sichtbar, da hier viele Neglekt-Patienten insbesondere dann extrem langsame Reaktionszeiten aufweisen, wenn ein linksseitiger Zielreiz invalide angezeigt wurde. Da in Experiment 1 gezeigt werden konnte, dass Nikotin die Aufmerksamkeitsreorientierung dann beschleunigt, wenn der Validitätseffekt groß ist, wurde erwartet, dass der Validitätseffekt für linksseitige Zielreize bei Neglekt-Patienten durch Nikotin verringert werden könnte. Dieser pharmakologische Effekt konnte bei einer Untergruppe von Patienten beobachtet werden und war von dem Ort der Hirnschädigung abhängig.

1. Theoretical Section

1.1 Visuospatial selective attention

1.1.1 Basic cognitive processes

The term ‘attention’ in everyday speech is used to describe a state of concentration or wakefulness. In psychological research, however, attention is a comprehensive construct covering diverse functions. A common distinction is made between the intensity, selectivity and supervisory (executive) aspect of attention (see figure 1 A for an exemplary taxonomy).

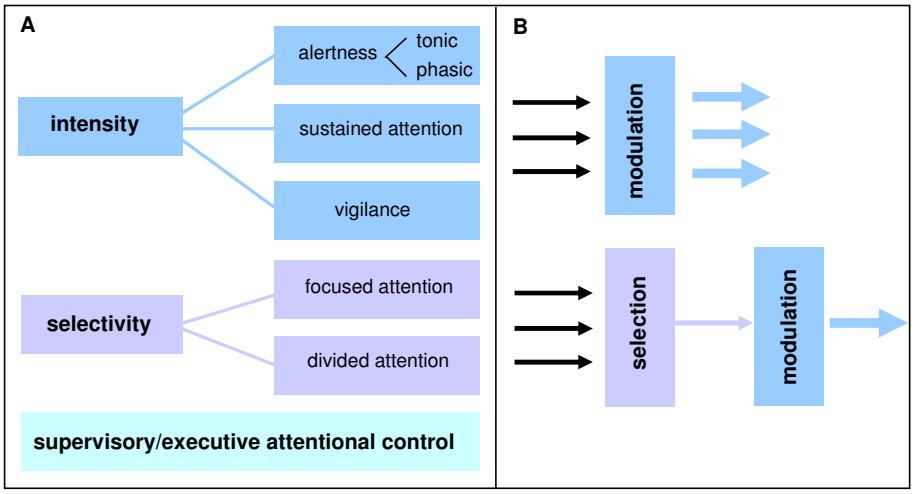

Figure 1. A) Illustration of the different components of attention (modified after van Zomeren & Brouwer, 1994). B) Illustration of the difference between the intensity and selectivity aspect of attention.

The intensity aspect of attention comprises phasic and tonic alertness (as measured with simple reaction time tasks with or without warning cue stimuli), sustained attention and vigilance (as assessed with monotonous signal detection tasks with a high or low event rate in which attention has to be maintained over a longer period of time) (Sturm, 2005). These functions non-

selectively enhance the processing of incoming stimuli (i.e., stimuli are detected faster and with fewer omissions if the subject is more alert or vigilant) (see figure 1B).

Usually, our environment provides us with a multitude of simultaneous sensory events, so that only a small fraction of these stimuli can be processed and reaches our awareness (Treue, 2003). Another function of attention is thus to select certain stimuli for further processing. In other words, selective attention '…implies withdrawal from some things in order to deal effectively with others…' (James, 1890; p. 404). Focused attention refers to processes in which attention is deployed to specific stimuli or stimulus features (measured, for example, with choice reaction tasks or tasks with distracting stimuli), while divided attention requires the distribution of attentional resources to multiple 'information channels' (as, for example, in dual task paradigms) (Sturm, 2005). Thus, with selective attention some stimuli are selected among a stream of incoming stimuli and are processed more thoroughly (see figure 1B).

Attentional selection can be accomplished either voluntarily (*top-down selection*) or by salient sensory stimuli which capture attention automatically (*bottom-up selection*) (see e.g., Jonides, 1981). As processing resources are capacity-limited, this selection necessarily takes place at the expense of other stimuli (see e.g., Desimone & Duncan, 1995). Thus, one current conception is that attention creates 'a representation of the environment that weighs every input by its local feature contrast and its current behavioural relevance' (= 'integrated saliency map'; Treue, 2003; p. 430).

Attention can, for example, be focused on a particular location in the visual field (*visuospatial attention*) leading to enhanced (i.e., faster and more efficient) perception in this part of space. This spatial orienting has been described as an attentional 'spotlight' (Jonides, 1980), 'zoomlens' (Eriksen & Yeh, 1985) or 'gradient' (LaBerge & Brown, 1989). Jonides (1980, 1983) proposed that subjects can allocate their attentional resources in two alternative modes. In the distributed mode resources are shared equally among candidate locations. However, the presence of a spatial cue, for example, can lead to a focusing of resources. By providing more rapid information processing at the

cued location this focused mode of attention bears analogy to a spotlight. Seizing this suggestion Eriksen and Yeh (1985) developed a 'zoomlens' model of attention emphasizing that the area of focal attention can be continuously increased or decreased according to task demands. LaBerge and Brown (1989) argued against a moving spotlight-model and instead proposed a gradient model of processing resources according to which gradient peaks are formed at the attended location in space.

Orienting of attention in space can occur independently of the position of the eyes since persons can maintain their gaze at a given point in space while covertly attending to another spatial location (von Helmholtz, 1866/1924, Posner, 1980). Similarly, attention can be covertly reoriented in space if a salient or behaviourally relevant stimulus appears at an unattended location. These orienting and reorienting processes can be investigated experimentally with the location-cueing paradigm (Posner, 1980; see figure 2).

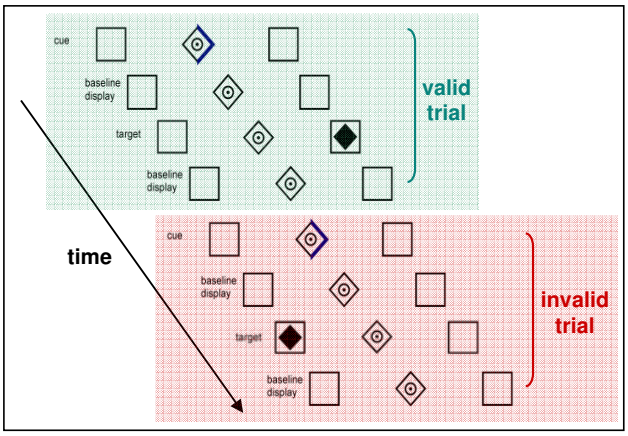

Figure 2. Illustration of the event sequence during valid and invalid trials in the location-cueing paradigm.

In this task, the subjects are presented with a central fixation point and two peripheral boxes. They are asked to respond as quickly as possible by button presses to target stimuli that appear in these boxes. In the simplest form of the task, subjects have to press one button as soon as they detect the target (cued target detection task). However, one can also use discrimination tasks

employing two target stimuli (e.g., a square and a circle) and two response buttons, accordingly. Importantly, the target stimuli are preceded by spatial cues that predict the location of the target with a certain probability (usually with ~80% in case of centrally presented cues). Thus, the cue is valid in some and invalid in other trials.

Figure 3 depicts the typical reaction time (RT) pattern which is observed in this paradigm. Compared to a neutral condition in which the cue does not provide any spatial information (e.g., points to both lateral boxes), target detection is faster if the target appeared at the cued location (i.e., in valid trials). Conversely, RTs are slower in invalid trials. The difference in RTs to invalidly and validly cued targets is termed the 'validity effect' and used as a behavioural measure for reorienting of attention. In other words, the validity effect reflects the time needed for disengaging attention from the invalidly cued location and shifting and engaging it at the target location (Posner, 1980).

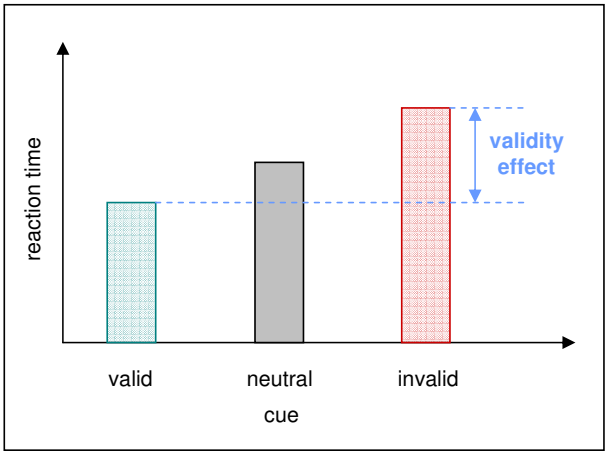

Figure 3. Prototypical reaction time pattern illustrating the validity effect in the location-cueing paradigm (fictitious data).

The validity effect is observed in paradigms in which short peripheral non-predictive cues (e.g., a short brightening of one of the lateral boxes) are employed to elicit automatic (exogenous) orienting of attention as well as in paradigms with central predictive cues (see figure 2) inducing voluntary

(endogenous) attention shifts (Posner, 1980; Jonides, 1981). In the endogenous version of the location-cueing paradigm, the ratio of validly to invalidly cued targets (i.e., cue validity) affects the size of the validity effect: if the information provided by the cue is highly valid, RTs to valid targets decrease, while RTs to invalid targets increase (see also experiment 1) when compared to a low cue validity condition. Attentional gradient models explain this influence of top-down information on attentional orienting and reorienting by differential resource distributions resulting in more demanding reorienting in the context of highly valid cues (Madden, 1992).

1.1.2 Neuroanatomy

Which parts of the human brain are involved in the control of orienting and reorienting of visuospatial attention? Answers to this question are given by lesion as well as functional neuroimaging studies. In the 1980s, the work of Posner and co-workers showed that the processes of disengaging, shifting and engaging of attention are differentially impaired in neurological patients with different forms of brain injury (Posner, Petersen, Fox & Raichle, 1988). Lesions in parietal brain areas produce a lateralized deficit in the disengagement of attention from a particular location (Posner, Walker, Friedrich & Rafal 1984; see also 1.2.3). Patients with damage to the midbrain (superior colliculi and peritectal region) are slower in shifting the attentional focus to locations in the visual field (Posner, Rafal, Choate & Vaughan, 1985). The ability to engage attention in the contralateral hemifield is impaired in patients with damage to the thalamus (pulvinar) (Rafal & Posner, 1987).

Based on the findings of functional imaging studies Corbetta and Shulman (2002) proposed two cortical attention networks with different functions and anatomical location (see figure 4A): A bilateral dorsal fronto-parietal network consisting of the area adjacent to the intraparietal sulcus (IPS) and the frontal eye fields (FEF) is supposed to control the voluntary orienting of attention. A ventral right-hemispheric fronto-parietal network comprising the temporo-parietal junction (TPJ) and the ventral frontal cortex is involved in the reorienting of attention in response to unexpected or unattended events (like, e.g., invalidly cued targets in the location-cueing paradigm).

However, it has also been shown that similar ventral fronto-parietal networks are activated by infrequently occurring stimuli (e.g., ‘deviants’ in oddball paradigms) which do not necessarily require spatial attention shifts (see figure 4B). Thus, it is not clear whether these areas (IPS, TPJ, VFC) have a more general function in the detection of unexpected salient events (Serences, Shomstein, Leber, Golay, Egeth & Yantis, 2005).

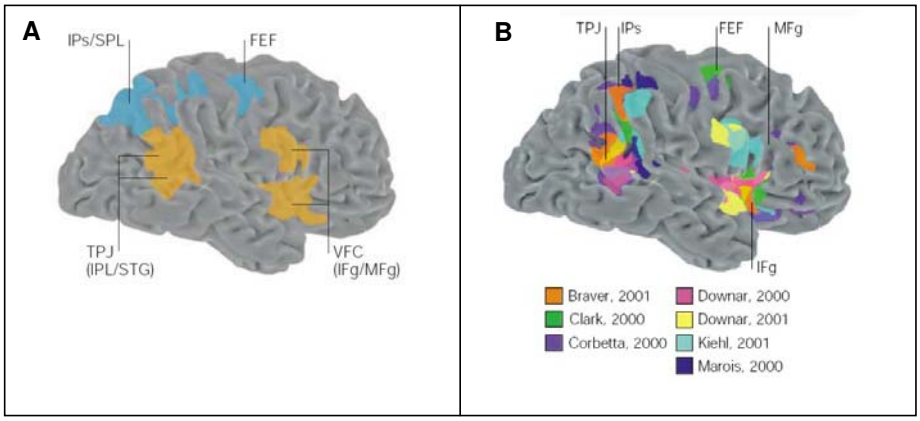

Figure 4. A) Dorsal *(blue)* and ventral *(brown)* fronto-parietal attention network. B) Activation of fronto-parietal brain regions in response to infrequently occurring (non-spatial) stimuli. (Figure 4A and B are adapted by permission from Macmillan Publishers Ltd: Nature Reviews Neuroscience; Corbetta, M. & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, *3*, 201-215; Copyright 2002).

1.1.3 Neurochemistry

There is compelling evidence that different cognitive functions are mediated by different neurotransmitter systems. Regarding attentional functions, Posner and Fan (2004) suggested that alerting (phasic non-spatial attention) and executive attention (e.g., resolving cognitive conflicts) rely on the noradrenergic and the dopaminergic system, respectively. Orienting and reorienting of attention, however, is supposed to be a cognitive function which is mediated by cholinergic neurotransmission.

In line with this assumption, studies in animals (Witte, Davidson & Marrocco, 1997; Phillips, McAlonan, Robb & Brown, 2000; Steward, Burke & Marrocco, 2001) as well as in humans (Witte et al., 1997; Murphy & Klein, 1998; Thiel, Zilles & Fink, 2005) have shown that cholinergic stimulants such as nicotine decrease RTs to invalidly cued targets and thus decrease the validity effect in the location-cueing paradigm (see figure 5). Conversely, lesions of the cholinergic neurons within the basal forebrain in monkeys result in slower attentional reorienting (Voytko, 1996). In healthy non-smoking subjects, the effect of nicotine is dependent on the size of the validity effect under placebo so that only those subjects that are slow in reorienting benefit from nicotine (Thiel et al., 2005).

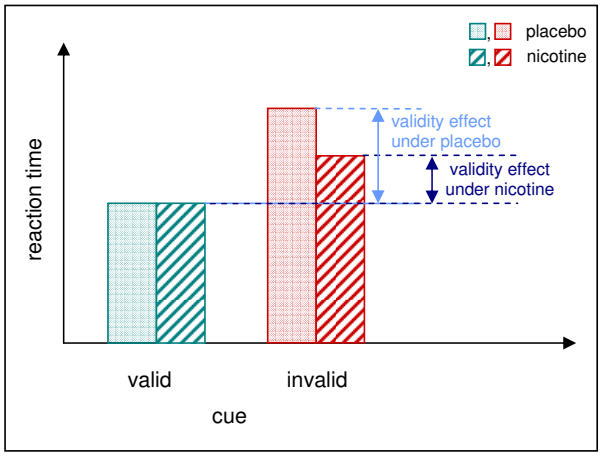

Figure 5. Proposed nicotinic effect on reaction times in the location-cueing paradigm (fictitious data).

The reduction of the validity effect under nicotine has been interpreted as a nicotine-induced facilitation of reorienting in response to behaviourally relevant events that occur outside the current focus of attention. At the neural level, pharmacological magnetic resonance imaging studies (see 1.3.3.) have shown that nicotine modulates reorienting-related activity in the parietal cortex (Thiel et al., 2005; Giessing, Thiel, Rösler & Fink, 2006). In particular, nicotine decreases neural activity in these areas during invalid trials. Another study (Hahn, Ross, Yang, Kim, Huestis & Stein, 2007) has suggested that nicotine reduces neural activity in areas belonging to the 'default network' of brain function (i.e., those areas that show higher activation in a baseline than in a task performance condition; see Gusnard & Raichle, 2001 for a review) and has proposed that nicotine potentates the alerting properties of external stimuli. Interestingly, a study by Giessing, Fink, Rösler & Thiel (2007) also identified activation patterns resembling the default network. Here, it was tested which of the brain areas that showed reorienting-related neural activity in the placebo session can be used to predict individual behavioural effects under nicotine.

The cholinergic neurotransmitter system consists of nicotinic and muscarinic receptors. Whereas cortical nicotinic receptors are mainly found in thalamic regions, the basal forebrain and sensorimotor areas, muscarinic receptors are more widely distributed throughout the brain (Gotti & Clementi, 2004; Zilles, Schleicher, Palomero-Gallagher & Amunts, 2002; see figure 6A).

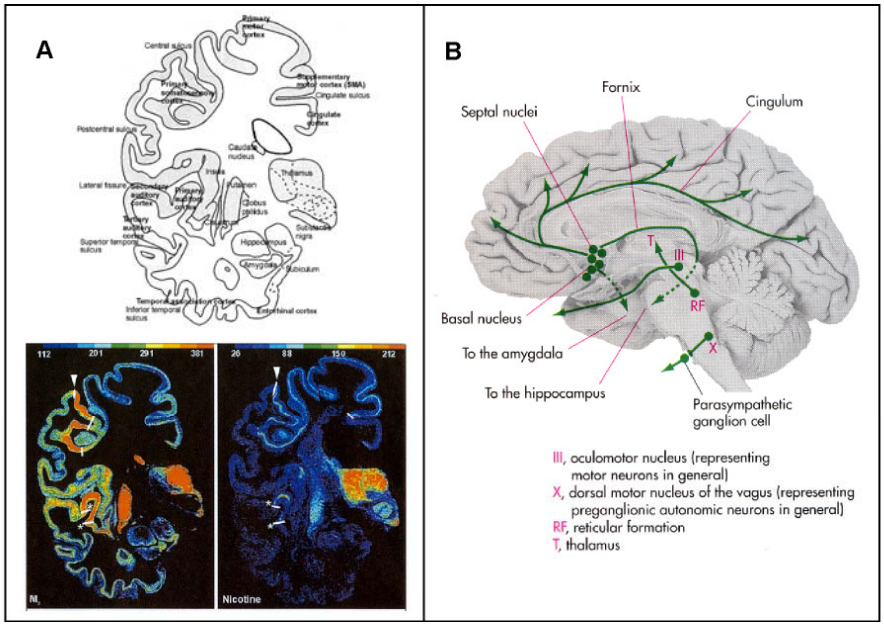

Figure 6. A) Distribution of muscarinic (M2) and nicotinic cholinergic receptors in the human brain (figures from Zilles et al., 2002; published in Brain Mapping: The Methods, Toga, A.W. & Mazziotta, J.C (Eds.). Quantitative analysis of cyto- and receptorarchitecture of the human brain, pp. 573-602; Copyright Elsevier 2002). B) Main cholinergic pathways in the human brain (this figure is reproduced with permission of Elsevier/Mosby and was published in Nolte, J. & Angevine. J. B. Jr. (2000*). The human brain in photographs and diagrams.* St. Louis: Mosby. Copyright Elsevier).

The main cortical cholinergic inputs emanate in the basal forebrain (see figure 6B), in particular in the Nucleus basalis of Meynert (basal nucleus). It has been proposed that these regions constitute an essential component of the cortical attentional networks affecting both signal-driven as well as top-down controlled stimulus detection (Sarter, Hasselmo, Bruno & Givens, 2005; see figure 7): The cholinergic input system within the basal forebrain can on the one hand be recruited by salient or novel stimuli (signal-driven modulation). On the other hand, the activity of the basal forebrain cholinergic system can be modulated by prefrontal brain areas in a top-down manner. Hence, the activity of the basal forebrain cholinergic system is regulated depending on interactions of the stimulus properties and of the attentional characteristics of a particular

cognitive task. Recently, a computational model of the role of the cholinergic system in balancing stimulus-driven and top-down-driven attentional selection has been established (Yu & Dayan, 2005). Here, it has been proposed that cholinergic agonists reduce the impact of top-down information in the location-cueing paradigm (see 2.2 and experiment 1)

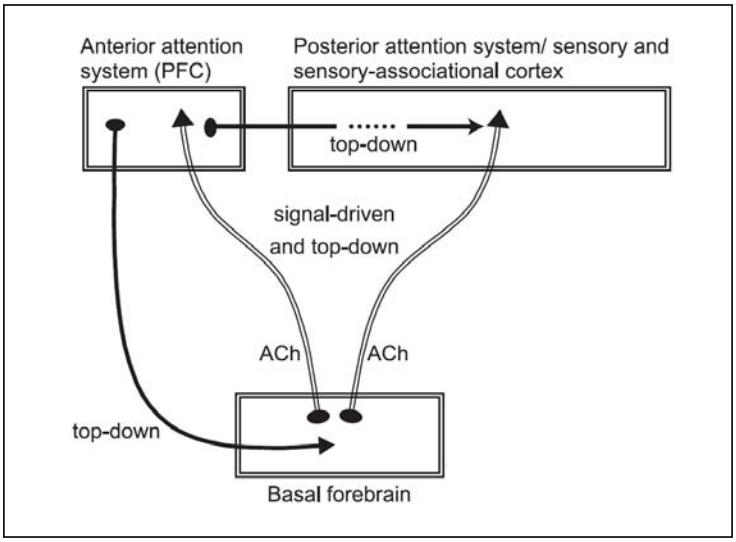

Figure 7. Cholinergic modulatory influence on cortical attention systems. *PFC:* prefrontal cortex, *ACh*: acetylcholine. (Reprinted from Brain Research Reviews, 48, Sarter, M., Hasselmo, M. E., Bruno, J. P. & Givens, B., Unraveling the attentional functions of cortical cholinergic inputs: interactions between signal-driven and cognitive modulation of signal detection, 98-111, Copyright 2005, with permission from Elsevier).

1.2 Spatial neglect

1.2.1 Clinical signs/Neuropsychology

Spatial neglect is a neurological syndrome that is characterized by reduced awareness of and by impaired responses to stimuli occurring on the side of space contralateral to the side of brain damage. By definition, these symptoms cannot merely be attributed to sensorimotor deficits (Heilman, Valenstein & Watson, 2000; Parton, Coulthard & Husain, 2004). Neglect is most commonly observed after lesions of vascular aetiology (i.e., cerebral infarction or haemorrhage) (Parton et al., 2004) and affects approximately 40-60% of patients with left-hemispheric and 50-70% of patients with right-hemispheric brain injury (Fink & Heide, 2004). In the majority of the cases, in particular after damage to the left hemisphere, the patients recover from neglect symptoms completely within a period of six months after the stroke (Hier, Mondlock & Caplan, 1983). However, in about 25-35% of the patients residual neglect symptoms can persist for years (Fink & Heide, 2004; Zarit & Kahn, 1974).

Neglect is a manifold syndrome in that neglect symptoms can occur in different reference frames (ego (person-centred)- and allocentric (object-centred) reference frame) and can affect all sensory modalities (e.g., visual, auditory and somatosensory modality) as well as personal and/or extrapersonal space. In severe cases, neglect behaviour can be visible with the naked eye: The patients direct their gaze preferentially to the ipsilesional side of space and are inattentive to objects or persons that are located in the contralesional side of space (Kukolja & Fink, 2006). A screening for neglect symptoms usually consists of the administration of paper-and-pencil-tests which require cancellation, bisection or drawing of objects (like, e.g., the Behavioural Inattention Test; Wilson, Cockburn & Halligan, 1987). Figure 8 illustrates neglect symptoms as assessed by some of these tests. Moreover, computerized tests that allow the analysis of manual response times in addition to omissions (like, e.g., the Testbatterie zur Aufmerksamkeitsprüfung TAP; Zimmermann & Fimm, 1992) enable a more sensitive and detailed assessment

of neglect behaviour in that more subtle lateral biases (like they occur, e.g., in chronic patients) can be detected.

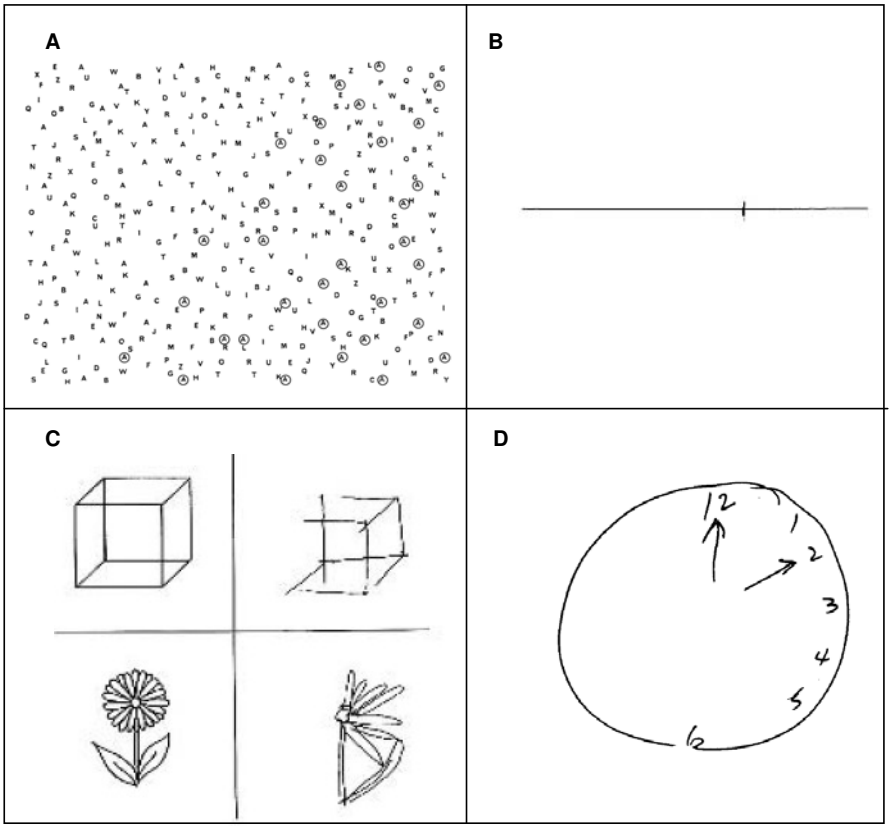

Figure 8. Neglect symptoms in a cancellation task (A, reprinted from Philosophical Transaction of the Royal Society of London, Series B, 354, Mesulam, M.M., Spatial attention and neglect: parietal, frontal and cingulated contributions to the mental representation and attentional targeting of salient extrapersonal events, 1325-1346, Copyright 1999, with permission of the Royal Society), a bisection task and a copying task (B and C, reprinted from Journal of Neurology, Neurosurgery and Psychiatry, 75, Parton, A., Malhotra, P. & Husain, M., Hemispatial Neglect, 13-21, Copyright 2004, with permission from the BMJ Publishing Group) and a drawing task (D, reprinted from Consciousness and Cognition, 7, Halligan, P.W. & Marshall, J.C., Neglect of Awareness, 356-380, Copyright 1998, with permission from Elsevier).

Various hypotheses about the pathomechanisms underlying spatial neglect have been proposed (for reviews see e.g., Fink & Heide, 2004; Halligan, Fink, Marshall & Vallar, 2003; Kerkhoff, 2001). All approaches usually share the view that the syndrome results from a higher-order spatial impairment (Vallar, 1998) that is, however, often associated with additional non-lateralized deficits (for a review, see Husain & Rorden, 2003). Some authors consider neglect to be an attentional disorder (see 1.2.3).

1.2.2 Neuroanatomy

In patients suffering from medial cerebral artery stroke a study of Mort et al. (2003) showed that the right angular gyrus of the inferior parietal lobe is commonly damaged in patients showing neglect symptoms. Neglect can, however, also be observed after damage to frontal (Husain & Kennard, 1996), superior temporal (Karnath, Frühmann-Berger, Küker & Rorden, 2004) and even subcortical (Karnath, Himmelbach & Rorden, 2002) brain regions. It has recently been suggested that the disruption of fronto-parietal fibres could play a crucial role in the neglect syndrome (fronto-parietal disconnection syndrome; Bartolomeo, Thiebaut de Schotten & Doricchi, 2007). Figure 9 summarizes candidate regions for the manifestation of neglect symptoms. Interestingly, there is evidence that the course of the symptoms differs between patients with different lesions as it has been shown that patients with frontal lesions recover more rapidly and completely than parietal patients (Stone et al., 1991).

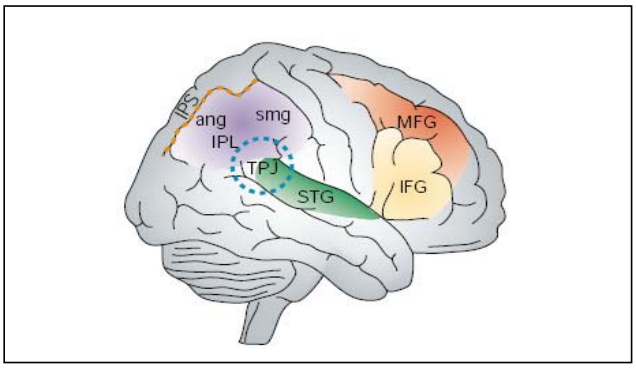

Figure 9. Brain areas that have been related to spatial neglect. *IPS:* intraparietal sulcus, *ang:* angular gyrus, *smg:* supramarginal gyrus, *IPL:* inferior parietal lobe, *TPJ:* temporo-parietal junction, *STG:* superior temporal gyrus, *MFG:* middle frontal gyrus, *IFG:* inferior frontal gyrus. (Adapted by permission of Macmillan Publishers Ltd: Nature Reviews Neuroscience. Husain, M. & Rorden, C. (2003). Non-spatially lateralized mechanisms in hemispatial neglect. *Nature Reviews Neuroscience*, *4*, 26-36; Copyright 2003).

1.2.3 Visuospatial selective attention in spatial neglect patients

The location-cueing paradigm (see 1.1.1) has been employed in brain damaged patients in order to investigate the neural mechanisms underlying visuospatial attentional reorienting (e.g., Posner et al., 1984; Friedrich, Egly, Rafal & Beck, 1998). It has been shown that patients with right parietal brain damage exhibit an asymmetrical RT pattern (see figure 10). These patients show disproportionate slow RTs when a left (contralesional) target was preceded by an invalid cue. Hence, it has been concluded that a deficit in reorienting attention from the ipsilesional to the contralesional side of space constitutes an important pathomechanism underlying the neglect syndrome (Posner et al., 1984).

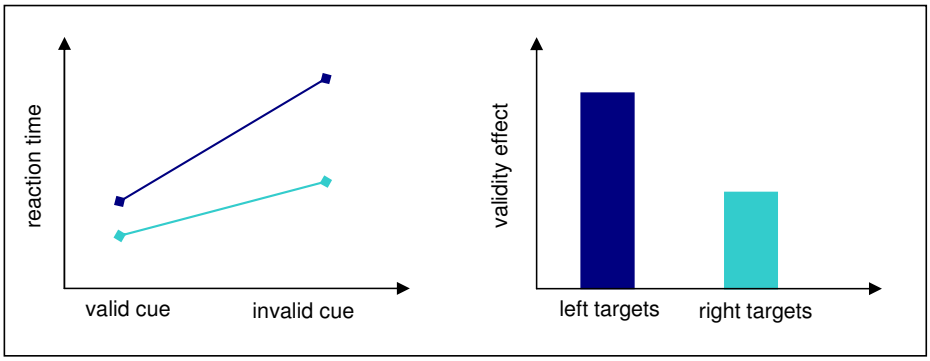

Figure 10. Typical reaction time pattern of neglect patients in the location-cueing paradigm. *blue*: targets appearing on the left side of space; *cyan*: targets appearing on the right side of space (fictitious data based on data from Posner et al., 1984 and Friedrich et al., 1998).

Since some neglect patients are able to voluntarily orient attention to contralesional space in valid trials, it has been suggested that this attentional impairment in neglect patients results from deficits in stimulus-driven (automatic) attention (Losier & Klein, 2001) like, e.g., an automatic attentional orienting bias towards the ipsilesional hemifield (Gainotti, D'Erme & Bartolomeo, 1991) in addition to the reorienting deficit. It has been reported that the reorienting deficit is more pronounced in location-cueing paradigms with shortly

presented peripheral cues (exogenous orienting mode, Losier & Klein, 2001). However, the use of peripheral cues (like, e.g., a short brightening of one of the lateral boxes) can cause problems in studies in neglect patients because left and right-sided peripheral stimuli are presumably processed differentially. Although attentional orienting can take place in the absence of conscious awareness of the cue (e.g., McCormick, 1997), it is questionable if the cognitive mechanisms are comparable for the two hemifields if left-sided peripheral cues are not consciously perceived. In other words, with peripheral cues the deficit in detecting the cue cannot clearly be separated from the deficit in target detection. Thus, as in the studies in healthy subjects of this thesis (experiments 1 and 2), central cue stimuli were used in the present patient study (experiment 3). Prior studies have shown that the reorienting deficit can also be observed with central cues, suggesting that despite relatively preserved voluntary orienting of attention (facilitated target detection after valid cues even in the contralesional hemifield), the patients cannot entirely compensate for their contralesional impairment (Natale, Posteraro, Prior and Marzi, 2005). Thus, the RT pattern observed in the location-cueing paradigms with central cues probably results from an interaction of automatic and top-down controlled processes.

It should be noted that the increased validity effect for left-sided targets of neglect patients resembles the effect of high cue validity in the location-cueing paradigm in healthy subjects (see 1.1.1 and experiment 1). Although the mechanisms causing this slower attentional reorienting may be different (higher top-down expectation due to high cue validity in healthy subjects versus automatic allocation of attentional resources to the ipsilesional side in patients) and although high cue validity does not induce lateralized effects, both conditions are characterized by slower RTs in invalid trials indicating more demanding reorienting processes. Thus, making allowance for these restrictions, the effect of increasing cue validity in the location-cueing paradigm in healthy subjects can be regarded as a model for the reorienting deficit of neglect patients.

1.2.4 Therapeutic approaches

As the presence of neglect symptoms predicts poor recovery of function (Robertson & Halligan, 1999; Cherney, Halper, Kwasnica, Harvey, & Zhang, 2001) and complicates the rehabilitation process (Halligan & Cockburn, 1993), many attempts have been made to ameliorate neglect behaviour in the affected patients (for a review, see, e.g., Luauté, Halligan, Rode, Rossetti & Boisson, 2006 or Barrett et al., 2006). Interventions usually consist of neuropsychological trainings that either primarily target the patients' spatial deficits (e.g., visual scanning training, Weinberg et al., 1977; optokinetic stimulation, Pizzamiglio, Frasca, Guariglia, Incoccia & Antonucci, 1990) or their non-spatial impairments (e.g., sustained attention training; Robertson, Tegnér, Tham, Lo & Nimmo-Smith, 1995). However, it has also been shown that vestibular (Cappa, Sterzi, Vallar & Bisiach, 1987) or psychophysical stimulation (like e.g., transcutaneous electrical stimulation or neck muscle vibration; Karnath, 1994) can ameliorate the spatial bias in neglect patients. More recently, strategies like virtual reality training (Castiello, Lusher, Burton, Glover & Disler, 2004) and repetitive transcranial magnetic stimulation (rTMS, Oliveri et al., 2001) have been investigated in the modulation of neglect symptoms. To date, the above mentioned strategies have only short-term beneficial effects, i.e., the effects are restricted to a short time period after the intervention.

Only few attempts have been made to improve neglect-related cognitive deficits by means of pharmacological challenges which could provide the opportunity of a long-term administration accompanied by long-term beneficial effects. With regard to dopaminergic agents, equal numbers of studies have reported beneficial (Geminiani, Bottini, & Sterzi, 1998; Mukand et al., 2001) or adverse effects (Barrett, Crucian, Schwartz, & Heilman, 1999; Grujic et al., 1998), respectively. Malhorta, Parton, Greenwood & Husain (2006) recently reported beneficial effects of an acute administration of a noradrenergic agonist in a visual search paradigm in three neglect patients. The question whether stimulation of the cholinergic neurotransmitter system which has been proposed to mediate reorienting of attention can be beneficial in neglect patients has not been addressed yet. However, since it has been shown that neglect patients are slow in attentional reorienting towards contralesional targets (see 1.2.3) and

nicotine can reduce high validity effects in the location-cueing paradigm (Thiel et al., 2005; see also 1.1.3 and experiment 1, 2nd part), there is strong evidence to assume that neglect patients can profit from nicotine administration (see experiment 3).

1.3 Functional magnetic resonance imaging (fMRI)

1.3.1 Physical and physiological background

Magnetic resonance imaging (MRI) is one technique which allows the in vivo imaging of structure and function of the human brain. MRI measures the responses of hydrogen nuclei in a magnetic field (see e.g., de Haan & Rorden, 2007 for a review). Hydrogen nuclei are positively charged and as they are spinning around their own axis they have a magnetic moment. When put into a strong external magnetic field, the hydrogen nuclei align themselves in the direction of this field and precess with a frequency which is proportional to the strength of the field (Schild, 1997; Jezzard & Clare, 2001). The application of a radiofrequency (RF) pulse changes the orientation of the magnetic moment of the nuclei for 90° if its frequency equals the frequency of the precessing nuclei (i.e., if the two frequencies are resonant). When the RF pulse is terminated, the hydrogen nuclei return to their original orientation and thus emit energy which can be measured by voltage induction in a nearby placed coil. This process is termed relaxation (Jezzard & Clare, 2001). Different tissues (e.g., grey matter, white matter and cerebrospinal fluid in the brain) have different relaxation properties enabling the generation of images with different tissue-specific contrast (Horowitz, 1995; Jezzard & Clare, 2001).

Functional magnetic resonance imaging (fMRI) uses the MRI technique to measure changes in blood flow and blood oxygenation (in particular in the relative concentrations of deoxygenated and oxygenated haemoglobin) in the brain in response to changes in neuronal firing. Deoxygenated haemoglobin has paramagnetic properties and thus introduces inhomogeneity into a nearby magnetic field that can be measured with fMRI (de Haan & Rorden, 2007). In other words, deoxygenated haemoglobin acts as an endogenous contrast agent (Horwitz, Friston & Taylor, 2000). The changes in the fMRI signal have been termed the blood oxygen level dependent (BOLD) response (Ogawa, Lee, Kay & Tank, 1990). The time course of the BOLD signal in response to an increase in neural activity is called the haemodynamic response function (HRF). Thus, fMRI is an indirect method for assessing neuronal activation which relies on the

assumption of neurovascular coupling. However, it has been shown in monkeys that the HRF is strongly correlated with the signal from intracortical recordings of neural activity, in particular with changes in the local field potential (Logothetis, Pauls, Augath, Trinath & Oeltermann, 2001).

1.3.2 fMRI data analysis

The analysis of fMRI data can be subdivided in the preprocessing of the data and the subsequent statistical analysis of the signal changes due to experimental manipulations. The preprocessing usually comprises corrections for movement of the subject during scanning (realignment), for the order of slice acquisition (slice timing) and for intersubject anatomical variability (normalisation) as well as smoothing of the data (Friston, Price, Büchel & Frackowiak, 1997).

The statistical analysis consists of the comparison of one experimental condition relative to another or relative to a baseline, respectively. This is accomplished by application of the general linear model (GLM) which explains the variation of the fMRI signal in a particular voxel in terms of a linear combination of explanatory variables (experimental conditions, regressors) and an error term (Holmes & Friston, 1997). Thus, fMRI data analysis uses a univariate method in that tests are performed for each voxel in the brain separately. The analysis of fMRI data makes use of the cognitive subtraction method which was originally introduced into psychophysical reaction time analysis by Donders (1868/1969) to isolate cognitive operations. Table 1 illustrates this subtractive approach by means of the location-cueing paradigm. The identification of brain areas related to attentional reorienting (spatial domain) parallels the behavioural reaction time analysis (temporal domain, see 1.1.1) in that invalid trials are contrasted with valid trials [invalid > valid].

Table 1. Illustration of the cognitive subtraction approach by means of the location-cueing paradigm (modified after Wainwright & Bryson, 2005). Brain regions involved in attentional reorienting (disengage, shift, engage) can be isolated by contrasting invalid and valid trials.

experimental condition	cognitive processes in response to the cue	cognitive processes in response to the target
valid cue	shift to/engage at cued location	process target
neutral cue	prepare for target appearance	shift to, engage at target, process target
invalid cue	shift to/engage at cued location	***disengage from cued location, shift to/engage at target,*** process target
no cue		shift to/engage at target, process target

However, fMRI studies can also employ factorial designs which enable tests for interactions between experimental conditions and thus do not rely on the supposition of pure insertion (i.e., on the assumption that each cognitive component evokes a particular physiological activation independent from the current context; Friston, Price, Fletcher, Moore, Frackowiak & Dolan, 1996). Moreover, by means of a conjunction analysis (see, e.g., Friston, Penny & Glaser, 2005), it can be investigated whether cognitive processes share common neural correlates. Parametric designs furthermore allow testing for brain responses that vary monotonically with certain experimental parameters (Friston et al., 1997).

The statistical analysis of fMRI data is accomplished in two steps. First, the statistical analysis is done for each subject separately (so-called single subject or 1^{st}-level analysis) resulting in individual contrast images of the comparisons of interest. These contrast images are then entered in a group analysis employing a random effects model (2^{nd}-level analysis) to make population-based inferences.

1.3.3 Pharmacological MRI

The combination of psychopharmacology and fMRI, i.e., the investigation of neural activity related to an experimental task as a function of pharmacological manipulations, is called pharmacological MRI (Leslie & James, 2000; Honey & Bullmore, 2004; Thiel & Fink, 2006). The modulatory effects of a pharmacological agent can be explored either by comparing task-related neural activity under drug and under placebo in the same subjects (within-subject designs, cross-over designs) or by comparing different experimental groups which receive the drug or a placebo, respectively (between-subject designs). Both designs have their advantages and disadvantages: within-subject designs have to deal with problems related to repeated measurements (like, e.g., training and habituation effects) while in between-subject designs the two experimental groups must not differ in any other characteristics than the drug administered (Hills & Armitage, 1979; Millar, 1983).

Usually, one is interested in the interaction effect of a drug and an experimental condition (see figure 11), i.e., in the impact of a pharmacological agent on a circumscribed cognitive process like reorienting of attention.

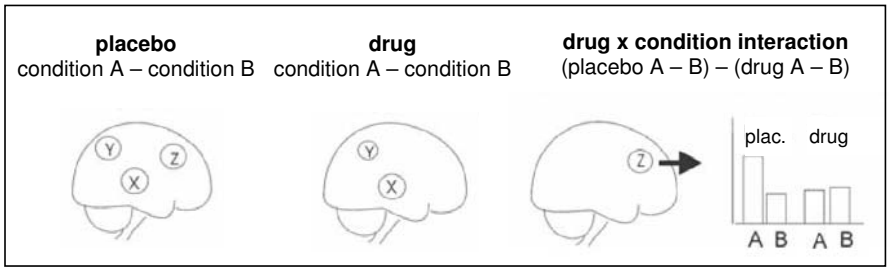

Figure 11. Illustration of the data analysis of a pharmacological fMRI study (Reprinted from Neurobiology of Learning and Memory, 80, Thiel, C., Cholinergic modulation of learning and memory in the human brain as detected with functional neuroimaging, 234-244, Copyright 2003, with permission from Elsevier).

Studying the effects of nicotine can in principle be done using cigarettes, intravenous injections, nicotine patches, oral snuff, chewing tobacco or nicotine chewing gums. These different forms of drug administration, however, have different pharmacokinetic characteristics (like, e.g., absorption rate and

maximum blood nicotine concentration). The advantage of the use of nicotine chewing gums, as realized in the present studies, is the easy and quick administration and the duration of the pharmacological effect: after approximately 30 minutes of chewing, the blood nicotine concentration stays on a relatively constant level for about 45 minutes (Benowitz, Porchet, Sheiner & Jacob, 1988; see figure 12). During that time, the subjects can perform the experimental task in the MR scanner.

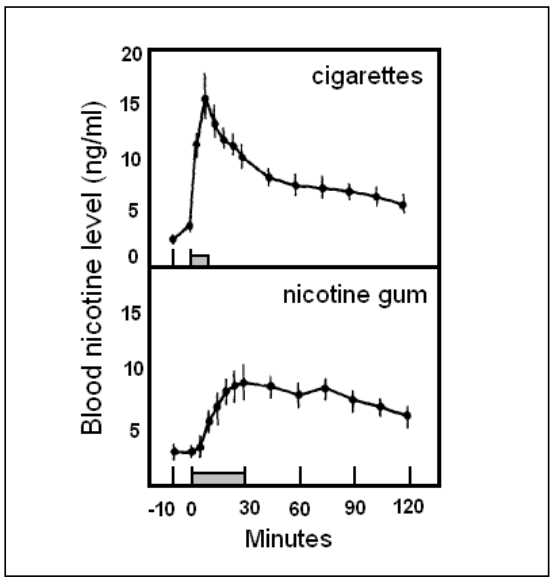

Figure 12. Blood nicotine levels after cigarette smoking and after 30 minutes chewing of a 4mg nicotine gum (Reprinted with permission from Macmillan Publishers Ltd: Clinical Pharmacology & Therapeutics, Benowitz, N.L., Porchet, H., Sheiner, L. & Jacob, P. (1988). Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison with cigarettes and nicotine gum. *Clinical Pharmacological Therapeutics, 44,* 23-28, Copyright 1988).

Since nicotine is a main component of tobacco smoke, studies in smokers and non-smoking subjects have to be performed differently and can possibly not be directly compared. Chronic smokers show a desensitization and an increase in the number of neuronal nicotinic receptors which has been proposed to contribute to nicotine addiction (Dani & Heinemann, 1996). Investigating the effects of the administration of nicotine in smokers requires smoking abstinence of the subjects for a circumscribed period prior to the experiment. In this case the effect of nicotine on a cognitive process per se is confounded with the reduction of withdrawal symptoms. Thus, studying the cognitive effects of nicotine in non-smoking subjects allows a more unambiguous interpretation of the data.

One key issue of pharmacological MRI is the impact of the respective drug on the neurovascular coupling. Drugs that have direct vascular effects may compromise the validity of the fMRI technique because the inference from blood flow measures to neuronal activity may be confounded. With regard to nicotine, however, it has been shown that it does not affect the BOLD response in visual areas (Jacobsen, Gore, Skudlarski, Lacadie, Jatlow & Krystal, 2002) and the precentral, medial frontal and cingulate gyrus (Murphy et al., 2006). In addition, a recent study by Hahn et al. (2007) has used arterial spin labeling (ASL) to control for possible non-specific effects of nicotine on blood flow and neurovascular coupling. The authors did not observe any differences in BOLD and cerebral blood flow (CBF) responses in a flashing checkerboard and finger tapping paradigm between the nicotine and the placebo session. Also no differences in the absolute quantitative blood flow or CBF at rest where observed. Moreover, pharmacological fMRI studies employing the location-cueing paradigm have demonstrated a specific neural effect of nicotine in invalid trials (Thiel et al., 2005, Giessing et al., 2006) which can hardly be explained by a global effect of nicotine on the BOLD response.

2. Empirical Section

2.1 Objectives of the thesis

The present thesis aimed at investigating the neural correlates as well as the cognitive and pharmacological modulation of visuospatial reorienting of attention in healthy subjects and neglect patients. Three experiments were conducted to answer the following questions:

1. How are the neural correlates of attentional reorienting affected by the validity of the spatial cue (cognitive modulation) in the location-cueing paradigm (experiment 1, 1st part)?
2. Is there an interactive effect of the cognitive and the pharmacological modulation of attentional reorienting, i.e., do the behavioural and neural effects of nicotine depend on the validity of the spatial cue in the location-cueing paradigm (experiment 1, 2nd part)?
3. Do the brain regions related to attentional reorienting differ from those responding to infrequent and unexpected deviant stimuli (experiment 2)?
4. If nicotine reduces the validity effect when healthy subjects are slow in reorienting of attention (i.e., in a high cue validity condition; experiment 1, 2nd part), can a nicotinic stimulation also reduce the reorienting deficit in patients with chronic spatial neglect in the location-cueing paradigm (experiment 3)?

In experiment 1 the size of the validity effect in the location-cueing paradigm was experimentally varied and the effects of this manipulation on brain activation patterns (Vossel, Thiel & Fink, 2006) as well as on the cholinergic modulation (Vossel, Thiel & Fink, 2008) were tested. Different sizes of the behavioural validity effect were induced by using different cue validities (90% and 60% validity, respectively). It was hypothesized that reorienting in the context of high cue validity should lead to higher validity effects accompanied by

stronger reorienting-related activation in parietal brain regions. Moreover, since it has been shown that the behavioural effect of nicotine on attentional reorienting depends on the baseline size of the validity effect (Thiel et al., 2005), it was expected that nicotine would reduce the validity effect and parietal cortex activity in the 90% rather than in the 60% cue validity condition. This is also predicted by the computational model of Yu and Dayan (2005) which postulates that nicotine reduces the use of the top-down information provided by the spatial cues.

Since the modulation of the size of the behavioural validity effect was obtained by using different cue validities (i.e., frequencies of invalid trials) in experiment 1, it cannot be ruled out that the observed brain responses merely reflect the processing of unexpected and infrequently occurring stimuli. Hence, it was tested in experiment 2 whether the processing of invalidly cued targets and non-spatial deviant stimuli draw upon the same or different brain activation patterns (Vossel, Weidner, Thiel & Fink, submitted).

In Experiment 3 (Vossel, Kukolja, Thimm, Thiel & Fink, in prep.), patients with chronic spatial neglect were tested with a location-cueing paradigm under placebo and under nicotine to investigate whether a cholinergic stimulation can be used to ameliorate their reorienting deficit. Here, we hypothesized that nicotine should decrease the validity effect in particular for left-sided targets, since the effect of nicotine in healthy subjects is only found for high validity effects under placebo (Thiel et al., 2005 and experiment 1, 2nd part). Moreover, to explain the observed intersubject variability in this pharmacological effect we tested whether the effect depends on the lesion site of the patients.

Table 2 provides an overview over the three experiments and the related peer-reviewed journal articles of this thesis.

Table 2. Overview over the 3 experiments of the thesis and the associated peer-reviewed journal articles.

	without pharmacological challenge/under placebo	pharmacological modulation by nicotine
healthy volunteers (fMRI studies)	Vossel, S., Thiel, C.M. & Fink, G.R. (2006). Cue validity modulates the neural correlates of covert endogenous orienting of attention in parietal and frontal cortex. *Neuroimage, 32,* 1257-1264. Vossel, S., Weidner, R., Thiel, C.M. & Fink, G.R. (submitted). What is 'odd' in Posner's location-cueing paradigm? Neural responses to unexpected location and feature changes compared.	Vossel, S., Thiel, C.M. & Fink, G.R. (2008). Behavioral and neural effects of nicotine on visuospatial attentional reorienting in non-smoking subjects. *Neuropsychopharmacology, 33,* 731-738.
neglect patients (behavioural study)	----------	Vossel, S., Kukolja, J., Thimm, M., Thiel, C.M. & Fink, G.R. (in prep.). Nicotinic modulation of visuospatial attention in patients with chronic spatial neglect.

2.2 Experiment 1

2.2.1 Vossel, S., Thiel, C.M. & Fink, G.R. (2006). Cue validity modulates the neural correlates of covert endogenous orienting of attention in parietal and frontal cortex. *Neuroimage, 32,* 1257-1264.

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Cue validity modulates the neural correlates of covert endogenous orienting of attention in parietal and frontal cortex

Simone Vossel[1,2], Christiane M. Thiel[1,2,3], Gereon R. Fink[1,2,4]

[1] Institute of Medicine, Research Centre Jülich, 52425 Jülich, Germany

[2] Brain Imaging Centre West, Research Centre Jülich, 52425 Jülich, Germany

[3] Institute of Biology and Environmental Sciences, University of Oldenburg, 26111 Oldenburg, Germany

[4] Department of Neurology - Cognitive Neurology, University Hospital Aachen, 52074 Aachen, Germany

Keywords: visuospatial attention, cue validity, fMRI

Corresponding author:

Simone Vossel

Institute of Medicine, Research Centre Jülich

Leo Brandt Str. 5, 52425 Jülich, Germany.

Tel: +49 -2461-61-4007, Fax: +49-2461-61-2820, email: s.vossel@fz-juelich.de

Abstract

Parietal brain regions have been implicated in reorienting of visuospatial attention in location-cueing paradigms when misleading advance information is provided in form of a spatially invalid cue. The difference in reaction times to invalidly and validly cued targets is termed the 'validity effect' and used as a behavioural measure for attentional reorienting. Behavioural studies suggest that the magnitude of the validity effect depends on the ratio of validly to invalidly cued targets (termed cue validity), i.e., on the amount of top-down information provided. Using fMRI we investigated the effects of a cue validity manipulation upon the neural mechanisms underlying attentional reorienting using valid and invalid spatial cues in the context of 90% and 60% cue validity, respectively. We hypothesized that increased parietal activation would be elicited when subjects need to reorient their attention in a context of high cue validity. Behaviourally, subjects showed significantly higher validity effects in the high as compared to the low cue validity condition, indicating slower reorienting. The neuroimaging data revealed higher activation of right inferior parietal and right frontal cortex in the 90% than in the 60% cue validity condition. We conclude that the amount of top-down information provided by predictive cues influences the neural correlates of reorienting of visuospatial attention by modulating activation of a right fronto-parietal attentional network.

Introduction

Attention can be allocated in space covertly without accompanying movements of the head or the eyes (Helmholtz, 1886/1924; James, 1890). Orienting and reorienting of covert visuospatial attention can be investigated with location-cueing paradigms in which a cue provides either correct or misleading information about the location of an upcoming target. Stimulus detection is facilitated when the target appears at the expected, i.e., the validly cued location. The difference in reaction times to invalidly and validly cued targets is referred to as the 'validity effect'; it is regarded as an indicator for the costs of disengaging and shifting of attention from the cued to the uncued location (Posner, 1980).

Regarding the neural correlates of attentional reorienting, neuropsychological data as well as neuroimaging studies attribute particular importance to parietal cortex. Spatial neglect constitutes a complex neuropsychological syndrome caused by focal cerebral lesions in which patients fail to attend to, respond adequately to or orient voluntarily to stimuli in contralesional space (Halligan et al., 2003; Fink and Heide, 2004). It is most commonly observed in patients with right hemispheric lesions, particularly after damage to the inferior parietal cortex and the temporo-parietal junction (Vallar and Perani, 1986; Vallar, 2001; Mort et al., 2003). Posner et al. (1984) observed that patients with right parietal lesions show an abnormal contralesional delay when attention has to be redirected from a location on the ipsilesional (i.e., intact) side to the contralesional side of space. This suggests that a specific impairment of the disengagement operation of attention contributes to the spatial neglect syndrome and emphasizes the importance of right hemispheric parietal brain structures for this cognitive process.

Consistent with patient data, neuroimaging studies using location cueing paradigms have shown that the inferior parietal cortex and the temporo-parietal junction are activated by attentional shifts (Corbetta et al., 2000; Kincade et al., 2005; Thiel et al., 2004; Thiel et al., 2005). Corbetta and Shulman (2002), however, postulate two separable neural attentional systems with distinct functions and anatomical locations: One system is supposed to be involved in

the endogenous allocation of attention in response to an informative cue (top-down control). This system comprises the intraparietal sulcus and the frontal eye fields (dorsal fronto-parietal network) and is organized bilaterally. In contrast, the ventral fronto-parietal network comprises the temporo-parietal junction and the ventral frontal cortex and is activated by events that require redirecting of attention to stimuli that have been outside the focus of processing (i.e., unexpected events like, e.g., invalidly cued targets). This reorienting network is supposed to be lateralized to the right hemisphere.

Behavioural studies suggest that orienting and reorienting of attention are modulated by the amount of top-down information that can be derived from an informative cue. In particular, it has been shown that the ratio of validly to invalidly cued targets (i.e., cue validity) influences attentional allocation with high cue validities increasing the magnitude of the validity effect (Jonides, 1980, 1983; Eriksen and Yeh, 1985; Madden, 1992; Riggio and Kirsner, 1997). In other words, if the information provided by the cue is highly valid, reaction times to valid targets decrease while reaction times to invalid targets increase.

Space-based theories of attention comprising spotlight, zoomlens and gradient models, ascribe this effect to a differential distribution of attentional resources in response to validity manipulations (Jonides, 1980, 1983; Eriksen and Yeh, 1985, Madden, 1992). While the first two approaches can account for faster processing of targets preceded by a highly valid cue, they cannot easily explain why performance declines at an initially unattended location (i.e., in invalid trials). Hence, a gradient model was suggested as the appropriate framework for the characterization of the effects of different cue validities (Madden, 1992). According to this model, the distribution of attentional resources in response to a highly valid cue would have a higher peak at the cued and a lower tail at the unattended location than in a condition with low validity of the cue. This would make attentional reorienting more difficult and hence increase the validity effect for highly valid cues.

A different approach for explaining the effects of different cue validities is taken by Yu and Dayan (2005) who propose a computational model which specifies the role of different neurotransmitters for the balance of top-down

expectation and bottom-up sensory input. In this model behavioural data from location cueing paradigms are successfully simulated by uncertainty computations according to Bayesian statistical theory. Cue validity in this framework represents 'expected uncertainty' which is defined as the degree of unreliability of predictive relationships. Thus, expected uncertainty would be high in low cue validity conditions. Expected uncertainty is supposed to suppress the use of the spatial cue for making inferences about the upcoming target location.

To our knowledge no functional imaging study has systematically addressed the influence of a cue validity manipulation on the neural activation patterns related to reorienting in cued target detection tasks. One study (Giessing et al., 2005) investigated the neural activity in a low, middle and high cue validity condition. However, by using 100% cue validity in the high cue validity condition, the authors did not compare differential neural activation in invalid trials. Given the involvement of parietal cortex in reorienting visuospatial attention and the effects of top-down expectations on attentional reorienting we accordingly investigated whether parietal cortex activity is modulated by cue validity. To address this issue, we designed a modified Posner type task with 90% and 60% cue validity and hypothesized that parietal activation related to reorienting (invalid trials vs. valid trials) would be increased in the high as opposed to the low cue validity condition.

Materials and methods

Subjects

Thirteen subjects with no history of neurological or psychiatric disease gave informed consent to participate in the study. All subjects were right-handed as indexed by a handedness inventory (Oldfield, 1971). One subject was excluded from further analysis due to excessive head movement (> 3mm) during fMRI scanning. Therefore, data from twelve subjects were analysed (6 males, 6 females; age range 19-33 years; mean age 25.7 years). The subjects were investigated in the context of a pharmacological (between subject design) fMRI study. The analyses presented here focuses on those subjects who belonged to the placebo group only.

Stimuli and experimental paradigm

We used a cued target detection task with central predictive cueing (Posner, 1980; see figure 1). Stimuli were projected onto a screen in front of the participant in the MR scanner. Viewing distance was approximately 29 cm. Subjects were presented with two horizontally arranged boxes (4.9° wide and 13.9° eccentric in each visual field). A central diamond (2.5° eccentric in each visual field) was placed in between serving as a fixation point. Cues consisted of a coloured 100 ms brightening of one side of the diamond depicting an arrowhead pointing to one of the peripheral boxes. The cue was followed by the presentation of the target appearing for 100 ms in one of the boxes. To prevent temporal orienting, we used two cue-target intervals (400 and 700 ms). Subjects were asked to respond as quickly as possible to the target by a button press with the index finger of their right hand. Trials were presented every 1800 ms. One third of the trials were 'null events' (Josephs and Henson, 1999) where a baseline stimulus was displayed, leading effectively to variable stimulus onset asynchronies (SOAs) (i.e., 1800 ms, 3600 ms, 5400 ms, etc.).

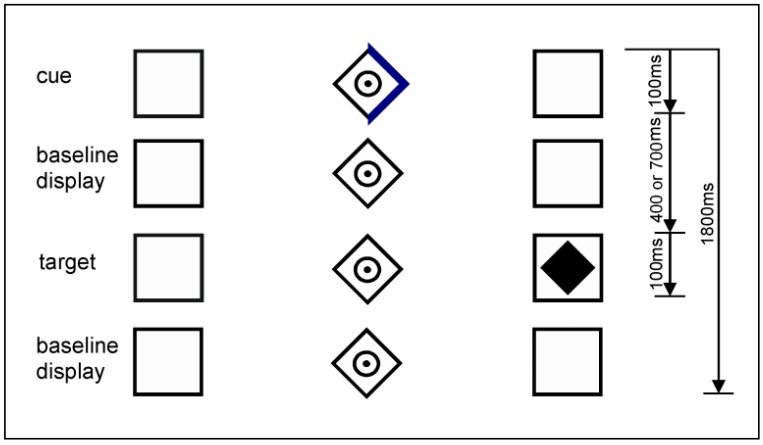

Figure 1. Experimental paradigm. Example of an event sequence during a valid trial. Trials were presented every 1800 ms. A trial consisted of a cue (100 ms) and a target stimulus (100 ms), separated by a 400 or 700 ms cue-target interval. Cues were either in blue or green colour and thereby indicated their predictive value to the subjects on a trial by trial basis. In invalid trials the target appeared in the opposite peripheral box. During null events only the baseline display was shown. Subjects were asked to fixate the central diamond throughout the experiment.

There were two differently coloured (green and blue) spatial cues that predicted the occurrence of a target with different validity (90% and 60%, respectively). The use of two different cues enabled the implementation of an event-related design in which trials could be presented randomly. In this regard our paradigm differed from those employed in prior behavioural studies where cue validity was changed only between different experimental blocks. Subjects were informed about the different cue validities and completed a practice session of 8 minutes prior to performing the task in the MR scanner. The assignment of cue colour (green or blue) and cue validity (90% or 60%) was counterbalanced across subjects. In addition to validly and invalidly cued trials we included catch trials in which the cue was not followed by any target. The experiment consisted of 756 trials including 252 null events and lasted for 24

minutes. The scanning session included two rest periods of approximately 1 minute during which the word 'pause' was shown on the display and the subjects were allowed to close their eyes. This was done to prevent deterioration of fixation ability due to exertion of the eyes. Restart of the task was indicated by a tone.

Data acquisition

T2*-weighted echoplanar (EPI) images with blood oxygen level-dependent (BOLD) contrast (matrix size 64 x 64, pixel size 3.12 x 3.12 x 5 mm^3) were obtained using a 1.5 T Sonata MRI System (Siemens, Erlangen, Germany). Seven hundred forty-five volumes of twenty-one 4-mm-thick axial slices were acquired sequentially with a 1.0 mm gap (repetition time 2.0 s, echo time 60 ms). The first 5 volumes were discarded to allow for T1 equilibration effects. To correct for interscan movement, images were spatially realigned to the first volume. Images were synchronized to the middle slice correcting for differences in slice acquisition time and normalized to a standard EPI template volume (resampled to 3 x 3 x 3 mm^3 voxels). The data were smoothed with a Gaussian kernel of 8 mm full-width half-maximum to accommodate intersubject anatomical variability.

Statistical analysis of imaging data

Data were analysed with Statistic Parametric Mapping software SPM2 (Wellcome Department of Imaging Neuroscience, London, Friston et al., 1995, http://www.fil.ion.ucl.ac.uk/spm2.html) employing a random effects model. Seven regressors were defined at the single-subject level comprising four events of interest (validly cued targets with 90% cue validity; invalidly cued targets in the context of 90% cue validity, validly cued targets with 60% cue validity, invalidly cued targets in the context of 60% cue validity) and 2 events of no interest (catch trials, incorrect responses). The event types were time-locked to the onset of the target by a canonical synthetic haemodynamic response function (hrf). The pauses were modelled as blocks (convolved with the hrf) in a

third regressor of no interest. The six movement parameters were included in the design matrix as additional regressors. Data were scan-wise scaled to reduce globally distributed confounding effects (Kiebel and Holmes, 2004) and high-pass filtered at 1/128Hz. Due to the low correlation between global mean and the contrast-weighted design matrices for both validity effects and the interaction contrast (see below) we can rule out that global scaling might have produced artificial deactivations (Aguirre et al., 1998; validity effect 90% cue validity: averaged absolute values of correlations r = 0.05; validity effect 60% cue validity: r = 0.04; interaction contrast (validity effect 90% > validity effect 60%): r = 0.04).

The respective 4 contrast images (each trial type vs. baseline) were entered into a 1 x 4 within-subjects ANOVA. Inhomogeneity of variance and correlation of measurements were estimated with a Restricted Maximum Likelihood (ReML) algorithm. We used the following directed t-contrasts to test our hypotheses. To assess neural activity related to attentional reorienting under 90% and 60% cue validity we contrasted invalidly with validly cued trials (invalid > valid) for each validity condition. For the comparison of different reorienting processes in response to different cue validities we contrasted the two validity effects (90% cue validity [invalid > valid] > 60% cue validity [invalid > valid]) with each other. Activations and figures from these analyses are reported at a level of $p < .001$ uncorrected and a cluster threshold of more than five contiguous voxels.

To compare the brain regions related to reorienting in the present experiment to previous studies we additionally conducted region of interest (ROI) analyses using the coordinates reported by Corbetta et al. (2000). We defined two spheres with a radius of 16 mm, each, centred at the voxel of peak activation in the inferior parietal cortex (talairach coordinates: x=53, y=-49, z=30) and superior temporal gyrus (x=57, y=-45, z=12) (WFU PickAtlas; Maldjian et al., 2003). Statistical images from these analyses were corrected for multiple comparisons across the search volume by using false discovery rate (FDR) inference to control for the expected proportion of false positives among suprathreshold voxels ($p_{FDR}<.05$) (Genovese et al., 2002).

Statistical analysis of behavioural data

Reaction times (RTs) faster than 100 ms (i.e., anticipations) were excluded from the analyses. As RT data usually contain slow outlying values resulting in positively skewed distributions, traditional RT analysis can cause misinterpretations (Heathcote et al., 1991). For this reason, we used a distributional analysis fitting ex-Gauss distributions to individual RT data (Heathcote et al., 2004). This technique has already been applied to RT data obtained from location-cueing paradigms (Gottlob, 2004) as well as the Stroop task (Heathcote et al., 1991). Ex-Gauss functions consist of a Gaussian component (with the mean μ and the standard deviation σ) and an exponential component τ. Probability density functions were plotted for the four experimental conditions according to the following formula:

$$f(RT) = \frac{e^{\frac{\sigma^2}{2\tau^2} - \frac{RT-\mu}{\tau}}}{\tau\sqrt{2\pi}} \int_{-\infty}^{\frac{RT-\mu}{\sigma} - \frac{\sigma}{\tau}} e^{-\frac{y^2}{2}} dy$$

The means of the Gaussian component (μ) for each subject were entered into a 2 x 2 repeated measures ANOVA with the factors cueing (valid; invalid) and cue validity (90%; 60%). In case of significant interactions we conducted post-hoc paired t-tests to elucidate the origin of these effects. Moreover, validity effects of the 90% and the 60% cue validity condition (RT invalid trials - RT valid trials) were post-hoc compared with a paired t-test. Additionally, these results were compared to a traditional RT analysis in which median RTs were calculated for all four trial types in each subject and tested with the same statistical tests as described above.

Eye movement control

Eye position was monitored during scanning with an MR-compatible infrared eye tracker (ASL Model 540, Applied Science Group Co., Bedford, MA). Eye data were analysed with ILAB software (Gitelman, 2002). Artefacts related to blinking were filtered out. A region of interest subtending 25% of the cue-target distance from the centre was defined as fixation zone. For each subject

and cue validity condition the amount of time spent in this central region between cue and target presentation was calculated.

Results

Behavioural data

Misses, anticipations and false alarms (catch trials) amounted 4.3%, 0.7% and 6.2%, respectively. There were no significant differences in incorrect responses between the two cue validity conditions. The results of the distributional RT analysis are shown in figure 2.

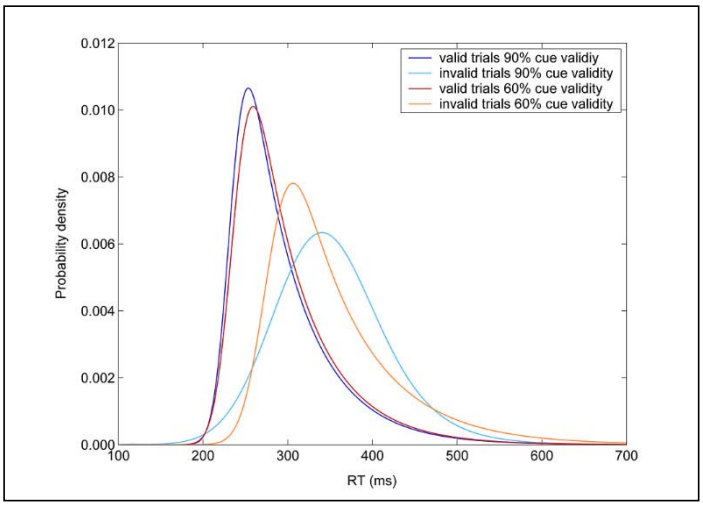

Figure 2. Behavioural data. Ex-Gauss distributions for the 4 experimental conditions (see Materials and methods for further explanation).

The 2 x 2 ANOVA for repeated measurements of the Gaussian components (μ) revealed a significant main effect of cueing (valid; invalid) ($F(1,11) = 33.32$; $p<.001$) reflecting faster reaction times to validly than to

invalidly cued targets. Additionally, we observed a significant main effect of cue validity (90%; 60%) ($F(1,11) = 13.56$; $p<.01$) and a cueing x cue validity interaction ($F(1,11) = 37.76$; $p<.001$). Post hoc t-tests revealed that subjects responded significantly faster to validly cued targets in the 90% than in the 60% cue validity condition ($t(11) = -2.30$; $p<.05$). Conversely, reaction times to invalidly cued targets in the 90% cue validity condition were significantly slower than to invalidly cued targets in the 60% cue validity condition ($t(11) = 4.88$; $p<.001$). There was a significant difference in the two validity effects (RT invalid minus RT valid) ($t(11) = 6.145$; $p<.001$; see figure 3). The traditional RT analysis using individual median RTs yielded similar results. RT data from both analyses are summarized in table 1.

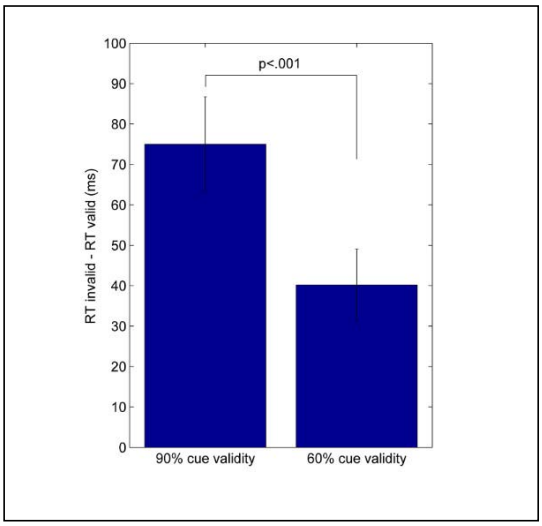

Figure 3. Behavioural data. Validity effect (RT invalid trials - RT valid trials) in the 90% and the 60% cue validity conditions. Error bars depict standard errors of the mean.

Table 1. Behavioural data. Means of the ex-Gaussian parameter μ (distributional analysis) and averaged median reaction times (traditional analysis) for the four experimental conditions. Reaction times are reported in milliseconds. Standard errors of the mean are shown in parenthesis.

	distributional analysis		***traditional analysis***	
	valid trials	**invalid trials**	**valid trials**	**invalid trials**
90% cue validity	233.0 (6.7)	308.0 (15.9)	276.0 (11.2)	344.4 (19.0)
60% cue validity	236.9 (7.2)	277.1 (13.3)	282.0 (11.0)	333.1 (14.6)

Eye movement data

For technical reasons, eye position data were not reliably recordable in six subjects. Analysis of the available eye data revealed that the participants spent on average 96.6 ± 1.8 % and 96.8 ± 1.9 % of the time during the cue-target interval within the central region of interest in the 90% and the 60% cue validity condition, respectively.

Neural data

Neural correlates of attentional reorienting were determined by contrasting invalid and valid trials separately for the two cue validity conditions. In the 90% cue validity condition stronger frontal activity in invalid as compared to valid trials was evident in the right middle frontal gyrus close to the inferior frontal sulcus (x=51, y=24, x=33; Z=3.40, 9 voxels). Three foci of activity were found in the right middle and superior temporal gyrus adjacent to the superior temporal sulcus (x=60, y=-9, z=15; Z=3.66, 6 voxels; x=63, y=-27, z=-9; Z=3.56, 5 voxels) with one cluster centred at the posterior part of the sulcus near the temporo-parieto-occipital junction (x=57, y=-57, z=15; Z=3.56, 18 voxels). Parietal activation was observed bilaterally along the intraparietal sulcus (x=54, y=-45, z=45; Z=3.92, 36 voxels; x=-42, y=-54, z=57; Z=3.86, 10 voxels). The activation in the right hemisphere extended into the supramarginal gyrus.

Additionally, regions in the right parahippocampal gyrus (x=33, y=3, z=-21; Z=4.53, 8 voxels; x=36, y=-9, z=-18; Z=3.53, 5 voxels) and the left thalamus (x=-21, y=-15, z=9; Z=3.83; 6 voxels) showed higher activation for invalidly than for validly cued targets. Activations related to reorienting (invalid > valid) in the 60% cue validity condition were located in the left middle frontal gyrus (x=-33, y=36, z=24; Z=4.24, 10 voxels) and the left intraparietal cortex (x=-36, y=-48, z=48; Z=3.41, 8 voxels).

To identify areas that were differentially activated during reorienting processes dependent upon cue validity we compared the two validity effects (90% cue validity [invalid>valid] > 60% cue validity [invalid>valid]) with each other. A list of all activations is provided in table 2. This contrast yielded two frontal clusters of activation located in the right middle frontal gyrus and the right inferior frontal gyrus nearby the inferior frontal sulcus. Additionally, a cluster in the right inferior parietal cortex, comprising parts of the intraparietal cortex as well as the supramarginal and the angular gyrus showed higher activation in the 90% cue validity condition (see figure 4). The parameter estimates at the voxel of peak activation revealed that this effect mainly resulted from differential activity in invalid trials. Further activation was observed in the right lingual gyrus.

Table 2. Brain areas showing higher validity effects in the 90% than in the 60% cue validity condition.

Region	Side	MNI-coordinates			Voxels	Z-score
		X	y	z		
inferior frontal gyrus	R	51	24	33	7	3.38
middle frontal gyrus	R	51	12	45	12	3.76
inferior parietal cortex	R	51	-54	48	96	4.25*
lingual gyrus	R	21	-81	-9	8	3.93

Activations are reported at threshold of p<.001 uncorrected. Activations denoted with an asterisk are also significant at p<.05 corrected for cluster level.

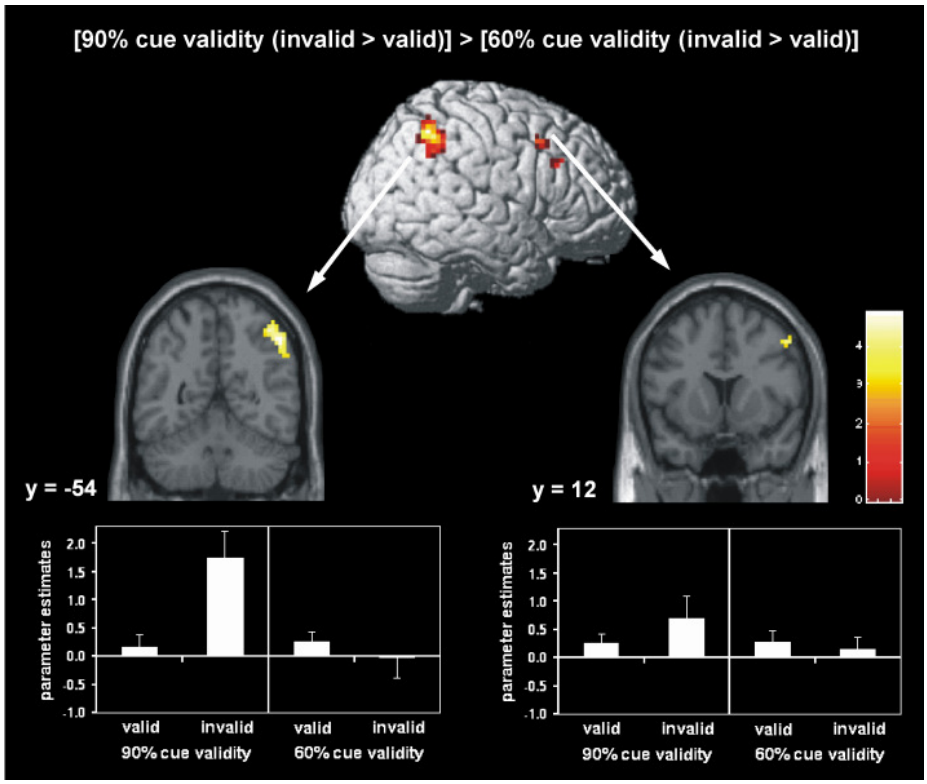

Figure 4. Brain areas showing higher activation to invalidly cued targets under the high validity as compared to the low validity condition.

ROI Analyses

The ROI analyses of areas related to attentional reorienting in the 90% cue validity condition revealed that four foci of activation were located adjacent to the inferior parietal cortex activation of Corbetta et al. (2000) whereof two foci were also enclosed in the ROI of the superior temporal gyrus (see table 3). However, the largest cluster of activation was located at the posterior part of the superior temporal sulcus near the temporo-parieto-occipital junction. Neither the right inferior parietal cortex nor the right superior temporal gyrus showed suprathreshold activation in the 60% cue validity condition.

Table 3. Results of two ROI analyses of reorienting in the 90% validity condition.

Region	Side	MNI-coordinates			Voxels	Z-score
		X	y	z		
inferior parietal cortex	R	54	-48	45	19	3.57
	R	57	-57	15	33	3.56
	R	45	-45	21	6	3.29
	R	51	-39	30	6	3.07
superior temporal gyrus	R	45	-45	18	2	3.68
	R	57	-57	15	18	3.56

A ROI analysis of the interaction contrast comparing reorienting in the 90% to the 60% cue validity condition illustrated that parts of the parietal activation fell into the inferior parietal area reported by Corbetta et al. (2000) (x=51, y=-54, z=45; Z=4.14, 83 voxels; x=57, y=-57, z=15 ; Z=3.05, 8 voxels; x=45, y=-45, z=21; Z=2.92, 1 voxel; x=51, y=-39, z=33 ; Z=2.74, 3 voxels; see figure 5). However, we did not find any activation within the ROI of the superior temporal gyrus as was observed when contrasting invalid and valid trials in the 90% cue validity condition.

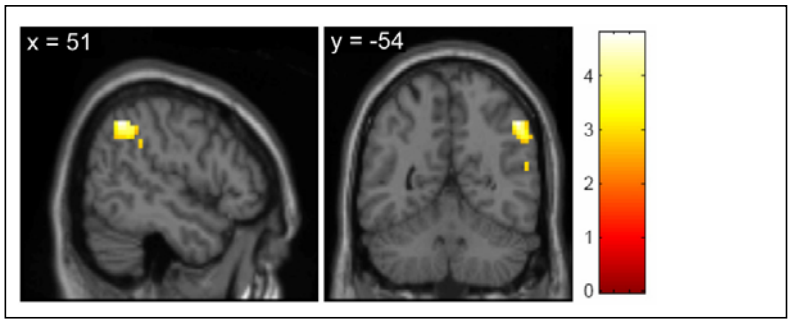

Figure 5. Results of the ROI analysis of the inferior parietal cortex comparing the two validity effects (90% cue validity [invalid > valid] > 60% cue validity [invalid>valid]).

Discussion

In the present fMRI study we manipulated cue validity in a cued target detection paradigm and investigated its effect upon the neural mechanisms underlying reorienting of attention. At the behavioural level, high cue validity increased and low cue validity decreased the validity effect. Our imaging data show that cue validity influences the neural correlates of reorienting visuospatial attention by modulating the activation of a right fronto-parietal attentional network.

Behavioural data

Our behavioural data revealed that cue validity significantly modulates the magnitude of the validity effect which is conceived as a measure for the costs of attentional reorienting. This result is in accordance with previous behavioural studies and additionally demonstrates that this effect can be observed even when trials are presented in a truly random fashion. The significant difference between the validity effects of the two cue validity conditions was evident in a distributional reaction time analysis in which ex-Gauss distributions were fitted for each subject and each experimental condition as well as in a traditional analysis of individual median reaction times. The responses to validly cued targets differed significantly between the two validity conditions corroborating that the subjects used the spatial cues for allocating their attention. However, the reaction time differences were more pronounced in invalid trials. These findings are in line with the assumption of a gradient model of attention attributing reaction time differences resulting from a cue validity manipulation to a differential distribution of processing resources (Madden, 1992). In response to a highly valid cue, resources are accumulated at the cued location accompanied with a withdrawal of resources from the uncued location making a subsequent disengagement more difficult. In contrast, a cue of lower validity entails a more flattened resource distribution with a lower maximum at the cued location and more available attentional resources at the uncued location resulting in relatively facilitated reorienting of attention. Our results are also consistent with the model of Yu and Dayan (2005) postulating a

relationship between the certainty of the information that can be derived from the spatial cue and the validity effect.

Neural data

Intraparietal sulcus/Inferior parietal cortex

Brain areas adjoining to the intraparietal sulcus were activated bilaterally with a more extensive activation cluster on the right hemisphere in the 90% cue validity condition. This finding is in line with previous imaging studies using central predictive cues, i.e., investigating reorienting in the context of endogenous allocation of attention, which employed cue validities of 75-80% (Corbetta et al., 2000; Kincade et al., 2005; Thiel et al., 2004, 2005). Thiel et al. (2004) found bilateral activation of the intraparietal cortex in response to invalidly as opposed to validly cued targets. Corbetta et al. (2000) separated cue- and target-related neural activity by using long cue-target intervals. They observed that the right hemispheric intraparietal cortex showed a significant validity effect. In contrast to the parietal activations under 90% cue validity, reorienting in the 60% condition did not elicit suprathreshold activation of the right parietal cortex in the present study, though subjects exhibited a significant validity effect as indexed by behavioural data. When comparing activity in the 90% and 60% condition we found clear evidence that neural activity in right parietal cortex was dependent on the validity of the spatial cue. In particular, this analysis yielded stronger activation of the intraparietal cortex as well as parts of the supramarginal and the angular gyrus in conditions of high top-down expectation. This result confirms the importance of this region for attentional reorienting processes. Consistent with this, the area activated in the present experiment represents one of the core regions for the manifestation of spatial neglect which according to the work of Posner et al. (1984) is characterized by a pronounced disengagement deficit. Particularly, a study of Mort et al. (2003) using high resolution MRI demonstrated that the area most commonly involved

in neglect resulting from middle cerebral artery stroke is located in the anteroventral part of the angular gyrus of the inferior parietal cortex. Other studies consider the adjacent region of the supramarginal gyrus as a key region for the manifestation of the neglect syndrome (Vallar, 2001; for a review, see Halligan et al., 2003). A patient study by Friedrich et al. (1998) demonstrated that inferior regions of the parietal cortex play a more crucial role for performance in location-cueing tasks than superior parietal structures.

The ROI analysis demonstrated that the observed parietal activation in this study is close to the temporo-parietal part of the ventral fronto-parietal network which is supposed to be involved in reorienting processes in response to unexpected events (Corbetta et al., 2000; Corbetta and Shulman, 2002). Note that it was assumed that this network should predominantly be engaged in reflexive, stimulus-driven (i.e., exogenous) orienting of attention which is usually operationalized with peripheral cues that are not predictive with regard to the location of the upcoming target. Using central predictive cues (cue validity > 50% in both conditions), however, we investigated reorienting in the context of two endogenous cues, i.e., after the voluntary allocation of attention in the present experiment. Interestingly, recent studies challenge the assumption that the temporo-parietal network is especially involved in stimulus-driven attention. Small et al. (2005) investigated the effects of monetary incentives (i.e., enhanced top-down control) on the performance in a cued target detection task with central cueing. The authors observed a significant relationship between activation of the right inferior parietal cortex and the amount of RT costs in response to invalid cues. This relationship was enhanced by monetary rewards. They concluded that the motivational incentive influenced the effort to disengage attention and that this effort was reflected in greater recruitment of the inferior parietal cortex. Kincade et al. (2005) compared the neural mechanisms related to reorienting under endogenous and exogenous conditions. Using comparable ROI analyses of areas of the ventral fronto-parietal network reported by Corbetta et al. (2000) the authors observed that the modulation of these areas was stronger in response to an invalid endogenous rather than an invalid exogenous cue. Consistently, subjects in the study of Kincade et al. (2005) showed bigger validity effects in the endogenous than in

the exogenous condition. The authors interpreted their results as reflecting the mismatch between expectation and sensory input in the endogenous condition.

Thus, an alternative explanation of our findings is that the observed activity in the temporo-parietal region may have resulted from a violation of expectancies rather than from more demanding attentional disengagement. Evidence for a differential modulation of spatially specific activity in occipital cortex in response to the two cues (like, e.g., observed by Hopfinger et al. (2000) when contrasting left- and right-sided cues) would argue for a differential distribution of attention and thus further strengthen our hypothesis that visuospatial reorienting is more difficult in response to a highly valid cue. However, the short cue-target interval and the unilateral target presentation (i.e., without a no-go stimulus on the opposite side), which were chosen in the present study from a psychological perspective, do not permit a separation of cue- and target-related neural activity. Consequently, we cannot investigate laterality effects any further. As invalid trials in the 90% cue validity condition are by definition less frequent than in the 60% condition and expectancy violation is presumably more prevailing under high cue validity, our study does not allow a clear-cut separation of expectancy mismatch and reorienting. Indeed, it has been observed that parts of the ventral fronto-parietal network elicit activation in response to novel or oddball stimuli that do not require visuospatial attention shifts (Linden et al., 1999; Kiehl et al., 2001; Downar et al., 2002). This suggests that these areas may play a more general role in signalling the unexpected appearance of relevant stimuli (Kincade et al., 2005) or coordinating top-down attentional control settings with incoming sensory information (Serences et al., 2005).

Superior temporal gyrus

Besides the inferior parietal cortex, parts of the superior temporal gyrus are regarded as belonging to the temporo-parietal junction. Activation of this area was found in the 90% cue validity condition, though the cluster was located near the temporo-parieto-occipital junction. Similar regions were also activated in studies investigating endogenous as compared to exogenous allocation of

attention (Kim et al., 1999; Mayer et al., 2004) or activity during attentional shifts compared to a baseline condition (Gitelman et al., 1999). It has been suggested that temporo-occipital areas are part of the top-down attentional system (Gitelman et al., 1999, Hopfinger et al., 2000) and that activation of these regions could reflect the inferred movement of the attentional focus to a specific location (Kim et al., 1999). Thus, the increased activity in response to invalidly cued targets in the present study may also result from augmented "movement" processes of the attentional focus rather than representing the disengagement component of reorienting. In this context it is noteworthy that we did not find any activation in the ROI of the STG when contrasting the validity effects of the two cue validity conditions. However, further research is needed to clearly separate the disengagement and shift component involved in the process of attentional reorienting.

Middle frontal gyrus/inferior frontal gyrus

Several frontal regions were activated in the present study. In the 60% cue validity condition, the left inferior frontal gyrus was significantly activated in response to invalidly cued targets. In the 90% cue validity condition, the right inferior frontal gyrus was activated and the comparison of the two validity effects yielded differential activation of two clusters in the right middle frontal gyrus and the right inferior frontal gyrus in the high cue validity condition. These regions are part of the prefrontal cortex which has previously been related to cognitive control processes (for a review, see Miller, 2000). Activation of the right middle and inferior frontal gyrus in location-cueing paradigms has been interpreted as reflecting evaluation processes of unexpected stimuli (Corbetta et al., 2002) or as inhibition of premature responses until reorientation is accomplished (Arrington et al., 2000). As in the case of the parietal activation, the differential activity in frontal areas was mainly caused by differences in invalid trials. One could thus speculate that invalid trials in the 90% cue validity condition required stronger inhibitory processes because of the high predictiveness of the cue. Moreover, recent research suggests a hierarchical model of prefrontal and parietal cortex function in cognitive control with prefrontal regions modulating

the activity in posterior brain regions (Brass et al., 2005; Miller and D'Esposito, 2005). We accordingly suggest that the activations observed in this study may reflect such an interplay between frontal and parietal brain areas.

Conclusion

The present fMRI study demonstrates that the neural mechanisms underlying reorienting of visuospatial attention are susceptible to cue validity manipulations in location-cueing paradigms and that the activation of a right-hemispheric fronto-parietal attentional network is modulated according to the probabilistic information of the spatial cue.

Acknowledgements

We are grateful to our colleagues from the MR and Cognitive Neurology groups for valuable support and discussions. CMT and GRF are supported by the Deutsche Forschungsgemeinschaft (KFO-112, TP 8).

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2.2.2 Vossel, S., Thiel, C.M. & Fink, G.R. (2008). Behavioral and neural effects of nicotine on visuospatial attentional reorienting in non-smoking subjects. *Neuropsychopharmacology, 33,* 731-738.

Behavioral and neural effects of nicotine on visuospatial attentional reorienting in non-smoking subjects

running title: Nicotine and attentional reorienting

Simone Vossel[1,2] MSc, Christiane M. Thiel[1,2,3] PhD, Gereon R. Fink[1,2,4] MD

[1] Institute of Neuroscience and Biophysics - Medicine, Research Centre Jülich, 52425 Jülich, Germany

[2] Brain Imaging Centre West, Research Centre Jülich, 52425 Jülich, Germany

[3] Institute of Biology and Environmental Sciences, University of Oldenburg, 26111 Oldenburg, Germany

[4] Department of Neurology, University Hospital Cologne, 50924 Cologne, Germany

Corresponding author:

Simone Vossel, Department of Medicine, Institute of Neuroscience and Biophysics,

Research Centre Jülich, Leo-Brandt-Str.5, 52425 Jülich, Germany

Tel: +49 -2461-61-4007, Fax: +49-2461-61-2820, email: s.vossel@fz-juelich.de

Abstract

The cholinergic neurotransmitter system has been proposed to be involved in the processing of probabilistic top-down information provided by endogenous cues in location-cueing paradigms. It has been shown that the behavioral and neural effects of a nicotinic cholinergic stimulation resemble the effects obtained by manipulating the validity of the spatial cues: Enhancing cortical nicotine levels and decreasing cue validity both reduce the reaction time difference between invalidly and validly cued targets (i.e., the 'validity effect') as well as neural activity related to attentional reorienting in parietal brain regions. In the present study we investigated whether the behavioral and neural effects of nicotine in location-cueing paradigms are dependent upon different a priori cue validities. Twenty-four subjects were investigated in a double-blind placebo-controlled between-subject design with functional magnetic resonance imaging (fMRI). Nicotine was administered to non-smoking volunteers via polacrilex gums (Nicorette®, 2mg) prior to performing a location-cueing paradigm with valid and invalid cues in the context of 90% and 60% cue validity in the MR scanner. Nicotine significantly reduced the validity effect in the 90% but not in the 60% cue validity condition. Fronto-parietal and cingulate regions showed stronger nicotinic reductions of reorienting-related neural activity in the high than in the low cue validity condition. Our data reveal an interaction effect between the pharmacological and cognitive modulation of attentional reorienting which is evident at both a behavioral as well as the neuronal level.

Keywords: neuropharmacology, acetylcholine, fMRI, selective attention, location-cueing paradigm, cue validity

Introduction

The cholinergic agonist nicotine has been shown to improve a variety of attentional processes in smoking and non-smoking human subjects (for a review, see, e.g., Newhouse et al, 2004 or Rezvani and Levin, 2001). One attentional function which is regarded to be mediated by cholinergic neurotransmission is reorienting of visuospatial attention (Posner and Fan, 2004). Attentional reorienting can be investigated in location-cueing paradigms when misleading advance information is provided by a spatially invalid cue. The difference in reaction times (RTs) to invalidly and validly cued targets is termed the 'validity effect' and is used as a behavioral measure for attentional reorienting. Human and animal evidence suggest that nicotine improves reorienting of attention since it was shown that nicotinic cholinergic stimulation reduces RTs to invalidly cued targets resulting in a reduction of the validity effect (Witte et al, 1997; Murphy and Klein, 1998; Thiel et al, 2005; Stewart et al, 2001; Phillips et al, 2000; see, however, Griesar et al, 2002).

Yu and Dayan (2005) recently proposed that the neurotransmitter acetylcholine signals 'expected uncertainty', i.e., the degree of unreliability of predictive relationships. Their model suggests that the reduction of the validity effect under nicotine is due to reduced reliance on top-down information provided by the cue. In other words, it is proposed that nicotine reduces the degree to which the spatial cue can be trusted and thus suppresses the use of the cue for attentional allocation. Thus, the behavioral effect of nicotine in location-cueing paradigms resembles the effect obtained by manipulating cue validity (i.e., the ratio between valid and invalid trials): Prior work has shown that decreasing cue validity increases RTs to validly cued targets and decreases RTs to invalidly cued targets (Jonides, 1980; Eriksen and Yeh, 1985; Madden, 1992; Riggio and Kirsner, 1997). Interestingly, this cognitive modulation of attentional reorienting has been observed in studies using peripheral cue stimuli which are thought to elicit automatic (exogenous) attentional orienting (Eriksen and Yeh, 1985; Madden, 1992) as well as centrally presented cue stimuli inducing voluntary (endogenous) attention shifts (Jonides, 1980; Riggio and Kirsner, 1997; Vossel et al, 2006). Regarding the pharmacological modulation

(i.e., the nicotine-induced reduction of the validity effect), existing animal and human studies have employed central predictive (Thiel et al, 2005), peripheral predictive (Witte et al, 1997; Murphy and Klein, 1998; Stewart et al, 2001) as well as non-predictive cues (50% cue validity; Phillips et al, 2000). However, with regard to human subjects, it has been shown that nicotine exerts its effect in paradigms with central predictive but not with peripheral non-predictive cueing (Meinke et al, 2006) suggesting that the top-down information about the cue-target relationship may play an important role in the pharmacological effect. One could speculate that findings from animal studies are thus not perfectly transferable to human research and with regard to the effects of cue validity manipulations on RTs divergent effects between humans and animals have indeed been reported (Bowman et al, 1993).

We have previously shown that both the manipulation of cholinergic neurotransmission and the manipulation of cue validity modulate reorienting-related brain activity in parietal and temporo-parietal areas (Thiel et al, 2005; Vossel et al, 2006). In particular, in these regions both nicotinic stimulation and low cue validity reduce neural activity related to attentional reorienting. The present study aims at investigating the nicotinic modulation of the validity effect in conditions of high and low cue validity. We employed a location-cueing paradigm with valid and invalid trials in the context of high and low cue validity (90% and 60%) and investigated reorienting-related neural activity under placebo and nicotine. We hypothesized that the modulatory effects of nicotine should depend on the a priori validity of the spatial cue with nicotine reducing the validity effect particularly in the context of high cue validity.

Materials and Methods

Subjects

The study was carried out in accordance with the ethical principles of the World Medical Association (Declaration of Helsinki). Twenty-six subjects gave written informed consent to participate in the study. All were right-handed as indexed by a handedness inventory (Oldfield, 1971) and had no history of neurological or psychiatric disease. To avoid confounding effects with withdrawal from nicotine all subjects had to be non-smoking since at least two years. No subject was on medication (except for contraceptives). Two subjects were excluded from further analysis due to excessive head movement (> 3 mm) during fMRI scanning. Therefore, data from twenty-four subjects were analyzed. To avoid confounding effects due to repeated measurements (Hills and Armitage, 1979; Millar, 1983) we used a between-subject design in which the subjects were randomly assigned to the nicotine or placebo group, respectively (placebo group: 6 males, 6 females; mean age 25.7 years; nicotine group: 7 males, 5 females; mean age 24.3 years). The data of the placebo group has been reported separately (Vossel et al, 2006).

Drug administration

Drug administration was double-blinded. The subjects received either a nicotine polacrilex gum (Nicorette® 2mg, Pharmacia/Pfizer) or a placebo gum with matched taste (Pharmacia/Pfizer) and chewed it for thirty minutes. They were instructed to chew once every 3 seconds. Pulse rate was assessed and blood samples were taken approximately twenty-five minutes after drug and placebo administration. Nicotine blood serum levels were determined after liquid-liquid-extraction using an isocratic high performance liquid chromatography (HPLC) with a reversed phase microbore column followed by UV detection. Subjective drug effects were assessed twenty minutes after drug administration with visual analogue scales for the three factors ‘alertness’, ‘contentedness’ and ‘calmness’ (Bond and Lader, 1974). Moreover, the subjects completed a symptom checklist asking for known negative side effects of nicotine.

Stimuli and experimental paradigm

We employed a location-cueing task with central predictive cues (Posner, 1980). Stimuli were projected onto a screen in front of the participant in the MR scanner with a viewing distance of approximately 29 cm. Subjects were presented with two horizontally arranged boxes (4.9° wide and 13.9° eccentric in each visual field). A central diamond (2.5° eccentric in each visual field) was placed in between serving as a fixation point. Cues consisted of a colored 100 ms brightening of one side of the diamond depicting an arrowhead pointing to one of the peripheral boxes.

There were two differently colored (green and blue) spatial cues that predicted the occurrence of the target with different validity (90% and 60%, respectively). The assignment of cue color (green or blue) and cue validity (90% or 60%) was counterbalanced across subjects. After a variable cue-target interval of 400 or 700 ms the cue was followed by the presentation of the target appearing for 100 ms in one of the two lateral boxes. Subjects were instructed to respond as quickly as possible to the target by a button press with the index finger of their right hand. Trials were presented randomly every 1800 ms. One third of the trials were 'null events' (Josephs and Henson, 1999) where a baseline stimulus was displayed, leading effectively to variable stimulus onset asynchronies (SOAs) (i.e., 1800 ms, 3600 ms, 5400 ms, etc.). In addition to validly and invalidly cued trials we included catch trials in which the cue was not followed by any target. The experiment consisted of 756 trials including 252 null events and lasted for 24 minutes. To prevent deterioration in fixation ability, the scanning session included two rest periods of approximately 1 minute during which the word 'pause' was shown on the display and the subjects were allowed to close their eyes. Prior to performing the task in the MR scanner the subjects were informed about the different cue validities and completed a practice session of 8 minutes.

Data acquisition

T2*-weighted echoplanar (EPI) images with blood oxygen level-dependent (BOLD) contrast (matrix size 64 x 64, pixel size 3.12 x 3.12 x 5 mm^3)

were obtained using a 1.5 T Sonata MRI System (Siemens, Erlangen, Germany). Seven hundred forty-five volumes of twenty-one 4 mm thick axial slices were acquired sequentially with a 1.0 mm gap (repetition time 2.0 s, echo time 60 ms). The first 5 volumes were discarded to allow for T1 equilibration effects and were thus excluded from further data processing. To correct for interscan movement, the images were spatially realigned to the first of the remaining seven hundred forty volumes. The images were synchronized to the middle slice correcting for differences in slice acquisition time and normalized to a standard EPI template volume (resampled to 3 x 3 x 3 mm^3 voxels). The data were smoothed with a Gaussian kernel of 8 mm full-width half-maximum to accommodate intersubject anatomical variability.

Statistical analysis of imaging data

Data were analyzed with Statistic Parametric Mapping software SPM2 (Wellcome Department of Imaging Neuroscience, London, Friston et al, 1995, http://www.fil.ion.ucl.ac.uk/spm2.html) employing a random effects model. For each subject seven regressors were defined comprising four events of interest (validly cued targets in the context of 90% cue validity, invalidly cued targets in the context of 90% cue validity, validly cued targets in the context of 60% cue validity, invalidly cued targets in the context of 60% cue validity) and 2 events of no interest (catch trials, incorrect responses). The event types were time-locked to the onset of the target by a canonical synthetic haemodynamic response function (hrf). The pauses were modeled as blocks (convolved with the hrf) in a third regressor of no interest. The six movement parameters (rigid body translation in the x-, y- and z-plane as well as rotation around the x-, y-, and z-axis) were included in the design matrix as additional regressors. For each subject four contrast images were created (each trial type vs. baseline). These first-level contrast images were entered into a mixed ANOVA model with the between-subject factor drug (placebo, nicotine). Inhomogeneity of variance and correlation of measurement were estimated with a Restricted Maximum Likelihood (ReML) algorithm. We focused our analysis on the effects of nicotine on reorienting-related neural activity dependent upon cue validity (i.e., the three

way interaction of the factors cueing x cue validity x drug), and used the directed t-contrast [placebo[90% cue validity[invalid>valid] > 60% cue validity[invalid>valid]] > nicotine[90% cue validity[invalid>valid] > 60% cue validity[invalid>valid]]] to isolate brain regions where nicotine reduces reorienting-related brain activity to a greater extent in the high as compared to the low cue validity condition. Activations are reported at a level of $p < .001$ uncorrected and a cluster threshold of more than three contiguous voxels and are shown on the mean image of the structural scans of all subjects. In addition, we correlated the parameter estimates (beta weights) for the voxel of peak activation in these regions with blood nicotine levels using Pearson's correlation coefficient.

Statistical analysis of behavioral data

For RT analysis we used a distributional analysis, fitting ex-Gauss distributions to individual RT data (Heathcote et al, 2004). As RT distributions are usually not normally distributed but positively skewed (Heathcote et al, 1991), this procedure allows a more comprehensive analysis of reaction time data and therefore provides a more detailed characterization of pharmacological effects than traditional RT measures, enabling for example the analysis of RT variability. Distributional RT analyses have already been applied in prior studies using location-cueing paradigms (Gottlob, 2004; Vossel et al, 2006). Reaction times (RTs) faster than 100 ms (i.e., anticipations) were excluded from the analyses. Ex-Gauss functions consist of a Gaussian component (with the mean μ and the standard deviation σ) and an exponential component τ. Probability density functions were plotted for the four experimental conditions according to the following formula:

$$f(RT) = \frac{e^{\frac{\sigma^2}{2\tau^2} - \frac{RT-\mu}{\tau}}}{\tau\sqrt{2\pi}} \int_{-\infty}^{\frac{RT-\mu}{\sigma} - \frac{\sigma}{\tau}} e^{-\frac{y^2}{2}} dy$$

A 2 x 2 x 2 mixed ANOVA model with the within-subject factors cueing (valid; invalid), cue validity (90%; 60%) and the between-subject factor drug (placebo; nicotine) was calculated for the parameters μ, σ and τ. Two-sample t-

tests were used to compare the validity effects (μ invalid – μ valid) as well as the number of missed responses between the placebo and nicotine group (in case of the validity effects a one-tailed significance was used due to our directed hypothesis of a reduced validity effect with nicotine). Moreover, we correlated the validity effect as well as the parameters μ, σ and τ with blood nicotine level scores using Pearson's correlation coefficient.

Eye movement control

Eye position was monitored during scanning with an MR-compatible infrared eye tracker (ASL Model 540, Applied Science Group Co., Bedford, MA). Eye data were analyzed with ILAB software (Gitelman, 2002). Artefacts related to blinking were filtered out. A region of interest subtending 25% of the cue-target distance from the centre was defined as fixation zone. We calculated for each subject and cue validity condition the amount of time spent in this central region between cue and target.

Results

Physiological and subjective measures

Nicotine significantly increased the pulse rate (placebo group: 68.8 ± 2.7 mean ± SEM, nicotine group: 78.2 ± 2.6, $t(22) = -2.5$, $p<.05$). Nicotine blood levels could be determined in eleven of the twelve subjects of the nicotine group and amounted to 3.57 ± 0.4 ng/ml. The data of one sample was lost due to technical problems. The result is comparable to a prior study on the effect of nicotine chewing gums on blood nicotine levels in healthy non-smokers using gums containing 4 mg of nicotine (i.e., twice as much as in the present study). Here, blood nicotine levels amounted on average to 6.53 ng/ml after thirty minutes of chewing (Nyberg et al, 1982).

There were no significant differences between the two groups with respect to their subjective ratings of alertness, contentedness and calmness. None of the subjects reported task-interfering side effects of the chewing gums (like, e.g., manifest feelings of nausea or dizziness).

Eye movement data

Eye movement data were reliably recordable in 14 subjects (six subjects of the placebo group and eight subjects of the nicotine group) only. Analysis of this data showed that there were no significant differences in fixation performance between the 90% and the 60% cue validity condition and the drug and placebo group, respectively (placebo group: 96.6 ± 1.8% and 96.8 ± 1.9%; nicotine group: 93.3 ± 4.5% and 93.6 ± 4.3%; all p-values > .5). Note that in all subjects fixation was additionally monitored by visual inspection of the participants' eyes during scanning.

Behavioral data

Missed responses, anticipations and false alarms (catch trials) amounted to 4.3%, 0.7% and 6.2% in the placebo and 1.9%, 0.5% and 5.6% in the

nicotine group, respectively. The difference in missed responses between the two groups was not significant ($p<.087$, all other p-values > .4).

Table 1. Behavioral data. Mean of the Gaussian component (μ) of the ex-Gauss distributions (± SEM).

	valid 90%	invalid 90%	valid 60%	invalid 60%
placebo	233.0 ± 6.7	308.0 ± 15.9	236.9 ± 7.2	277.1 ± 13.3
nicotine	241.2 ± 6.6	289.1 ± 13.0	246.2 ± 10.1	299.1 ± 14.2

The effects of cue validity (90% vs. 60%), cueing (valid vs. invalid) and drug (placebo vs. nicotine) were tested with ANOVAs on the parameters of the ex-Gauss RT distribution. Table 1 depicts the parameter μ (i.e., the mean of the Gaussian component) for each group and stimulus condition. We found a significant main effect of cueing ($F(1,22) = 64.49$; $p<.001$) reflecting faster RTs in valid as compared to invalid trials (i.e., the validity effect). The ANOVA further yielded a cue validity x drug interaction ($F(1,22) = 16.09$; $p<.001$) and a cueing x cue validity interaction ($F(1,22) = 6.07$; $p<.05$). Importantly, the three-way interaction of cue validity x cueing x drug was significant ($F(1,22) = 10.81$; $p<.01$) reflecting a differential nicotinic modulation of RTs in invalid trials in the 90% and 60% cue validity condition, respectively. Figure 1 illustrates this interaction in showing that nicotine specifically modulated the validity effect in the 90% cue validity condition ($t(22) = 1.85$; $p < .05$).

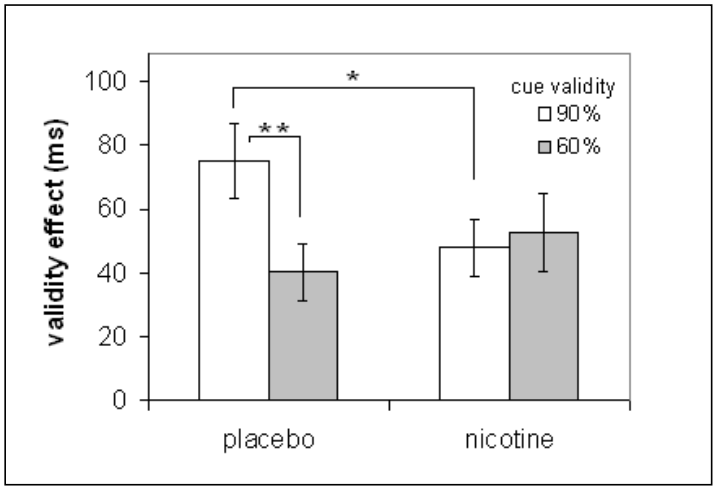

Figure 1. Behavioral data. Validity effects for the two cue validity conditions in the placebo and nicotine group. *p<.05; **p<.001.

For the parameter σ (i.e., the standard deviation of the Gaussian component of the RT distribution) we observed a significant main effect of cueing ($F(1,22) = 12.88$; $p<.01$) as well as cue validity x drug ($F(1,22) = 20.3$; $p<.001$) and cueing x cue validity x drug interactions ($F(1,22) = 14.04$; $p<.001$). This finding reflects that nicotine reduced RT variability in invalid trials in the context of 90% cue validity which is illustrated in figure 2. The ANOVA of the exponential component of the ex-Gauss function τ yielded significant cue validity x drug ($F(1,22) = 14.38$; $p<.001$) and cueing x cue validity x drug ($F(1,22) = 12.88$; $p<.01$) interactions. This result reflects a steeper decline in the probability function in invalid trials in the 60% cue validity condition under nicotine (see figure 2) indicating fewer outlying slow RT values.

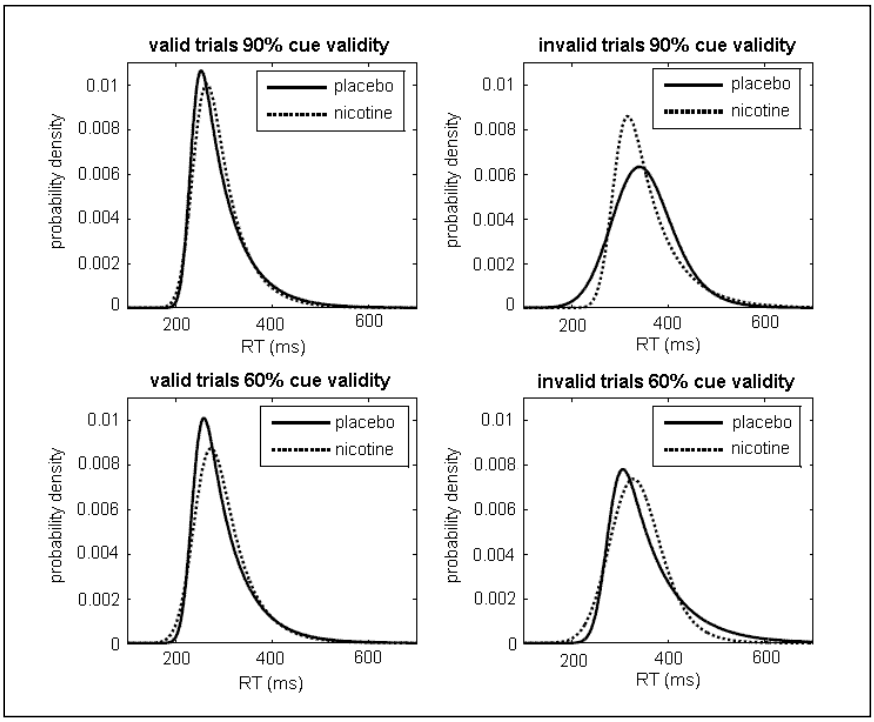

Figure 2. Behavioral data. Probability density functions for the four experimental conditions in the placebo and nicotine group.

No significant correlations between the size of the validity effect and blood nicotine level were observed. Interestingly, however, blood nicotine levels correlated negatively with the parameter σ in invalid trials in the 90% cue validity condition ($r = -.68$; $p<.05$, two-tailed significance) suggesting an association between increases in nicotine and the consistency of responding in this experimental condition.

Neural data

We identified those brain regions which showed stronger reductions of reorienting-related neural activity [invalid > valid] in the 90% than in the 60% cue validity condition in response to nicotine by a directed t-contrast capturing the interaction effect of the factors cue validity, cueing and drug. This contrast

revealed activation in temporo-parietal and parietal brain areas of the right hemisphere. The averaged parameter estimates (beta weights) for activations in these brain regions are plotted in figure 3 to illustrate BOLD signal changes in these brain areas as a function of drug, cueing and cue validity.

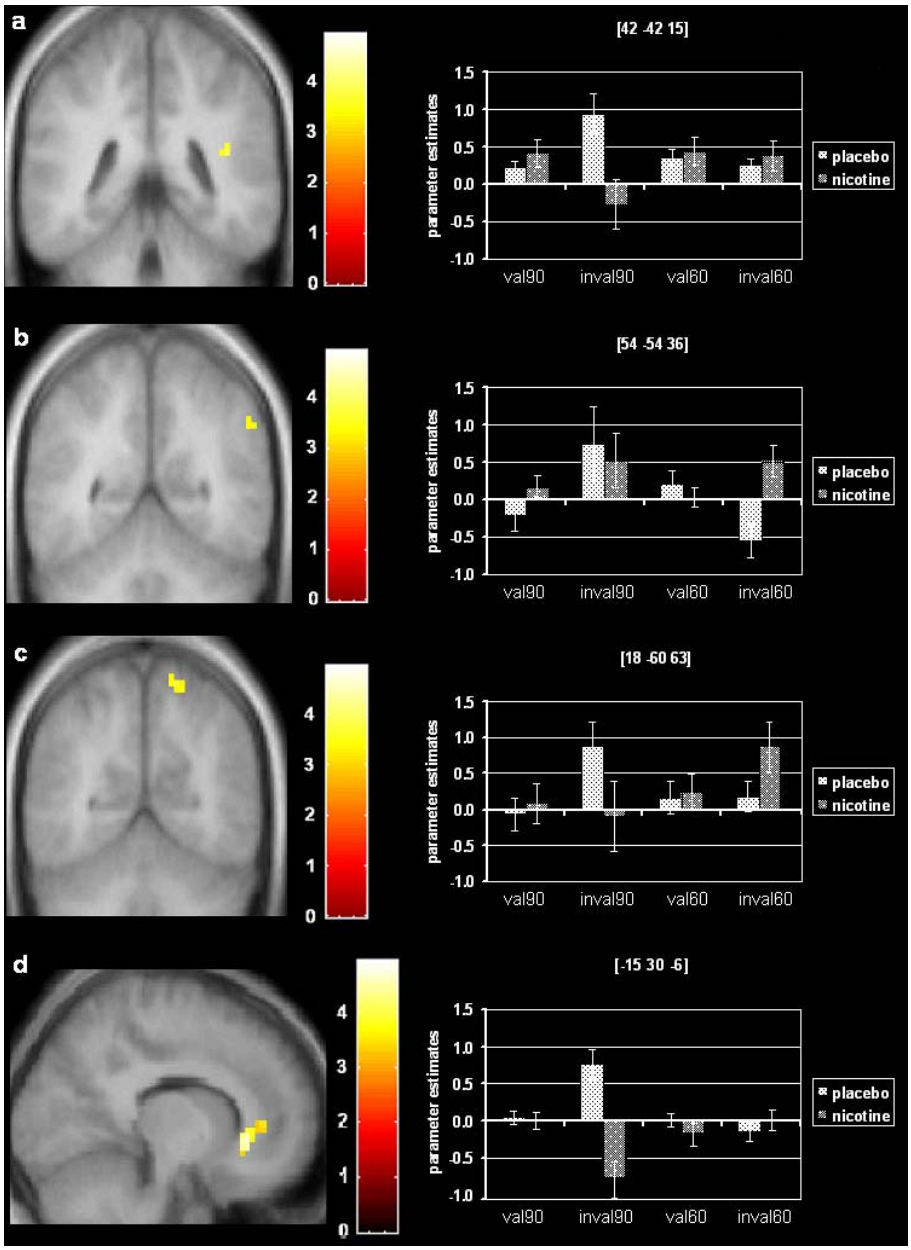

Figure 3. Coronal (a-c) and sagittal (d) sections through parietal, temporo-parietal and cingulate brain regions showing cueing x cue validity x drug interaction effects. a) right superior temporal gyrus/TPJ b) right angular gyrus c) right superior parietal gyrus/IPS d) left anterior cingulate gyrus. val90: valid trials 90% cue validity; inval90: invalid trials in the context of 90% cue validity; val60: valid trials 60% cue validity; inval60: invalid trials in the context of 60% cue validity.

Note that the increased BOLD signal in invalid trials in the 90% cue validity condition under placebo and its reduction under nicotine mirrors the behavioral data and is particularly evident near the right temporo-parietal junction (TPJ) and in the right superior parietal gyrus adjacent to the intraparietal sulcus. Interestingly, neural activity in invalid trials in the 60% cue validity condition showed the reversed pattern in the right angular and superior parietal gyrus with higher activity in the nicotine than in the placebo group. In addition, the interaction contrast yielded activation in right frontal brain regions as well as in a region in the left anterior cingulate cortex (see figure 3 d). A complete list of all activations obtained is provided in table 2. Significant correlations of neural activity with blood nicotine levels were observed for two brain regions (right precentral gryus and left middle temporal gyrus) only. Here, the activity in invalid trials in the context of high cue validity correlated negatively with the blood levels of nicotine (precentral gyrus: $r=-.73$, $p<.01$; middle temporal gyrus: $r=-.69$, $p<.05$). The latter correlation, however, was mainly caused by few outlying values.

Table 2. Neural data. Cortical regions showing stronger reductions in reorienting-related neural activity [invalid > valid] in the 90% than in the 60% cue validity conditions in response to nicotine.

Region	Side	MNI coordinates			Voxels	Z score
		x	y	z		
frontal						
superior orbital gyrus	R	15	54	-15	8	3.98
middle frontal gyrus	R	51	15	45	5	3.67
	R	36	60	3	6	3.39
precentral gyrus	R	51	0	24	4	3.65
temporal						
middle temporal gyrus	L	-51	-18	-21	3	3.25
superior temporal gyrus/TPJ	R	42	-42	15	3	3.60
parietal						
superior parietal cortex	R	18	-60	63	8	3.45
angular gyrus	R	54	-54	36	4	3.24
occipital						
superior lingual gyrus	R	24	-48	3	6	3.57
other						
anterior cingulate gyrus	L	-15	30	-6	30	4.53
hippocampus	R	33	-12	-18	6	3.35
white matter	R	30	-27	3	4	3.54
corpus callosum	R	3	9	15	9	3.53

The reverse contrast yielded one activation cluster in the left postcentral gyrus (x = -57, y = -18, z = 30; Z=3.57, 3 voxels).

Discussion

Using the combination of fMRI and psychopharmacology, we show that attentional reorienting in the location-cueing task is influenced by the cholinergic agonist nicotine specifically in situations of high cue validity. Brain areas contributing to this effect are right fronto-parietal as well as left anterior cingulate regions.

Behavioral data

The behavioral data demonstrate a decrease in the validity effect in the 90% cue validity condition after nicotine administration. The significant three-way interaction of the factors cueing, cue validity and drug suggests that a cholinergic facilitation of attentional reorienting is observed in situations of high cue validity only. Note, that for the 60% cue validity condition the magnitude of the validity effect was numerically even higher under nicotine. Furthermore, nicotine reduced the variability of RTs to invalidly cued targets in the context of high cue validity and this effect correlated with serum nicotine levels. Moreover, we observed a tendency towards fewer missed responses under nicotine.

Decreased RT variability and omission rates in response to nicotine have also been reported in a study using the Continuous Performance Test (CPT, Conners, 1995) which assesses sustained attention abilities (Levin et al, 1998). Although sustained attention is required for successful performance in location-cueing paradigms and presumably affects RT variability and missed responses, our results cannot solely be explained by increases in sustained attention. In particular, we did not observe a general speeding of RTs in the nicotine group. RTs in valid trials in the 90% and 60% cue validity condition as well as RTs in invalid trials in the low cue validity condition were numerically even higher in the group receiving nicotine (see table 1). However, as invalid trials occur per definition less frequently in a high than in a low cue validity condition, one could still argue that the observed nicotinic effect depends on stimulus frequency rather than on reorienting processes. Evidence against a dependence of the effect of nicotine on stimulus frequency is provided by a behavioral study (Meinke, 2006) which demonstrated that a low ‘go probability’ condition (in

which a response is required in a small proportion of trials only, i.e., to infrequent target stimuli) is not sufficient to evoke a nicotinic reduction of the validity effect. Our results therefore argue for a specific modulatory effect of nicotine on attentional reorienting (Witte et al, 1997; Murphy and Klein, 1998) which strongly depends on the a priori validity of the spatial cues.

We have previously suggested (Thiel et al, 2005) that the reduction of the validity effect under nicotine depends on the size of the validity effect under placebo. In the present study we manipulated the size of the validity effect experimentally by employing different cue validities. Using such a within-subject manipulation we were able to show that nicotine acts specifically in situations in which high validity effects are present. What determines the size of the validity effect? Attentional gradient models assume that processing resources are allocated according to the spatial cues and that this resource allocation is influenced by the validity of the cues (Madden, 1992). In a high cue validity condition the resource distribution has a strong peak at the cued location with only few resources at the uncued location leading to high validity effects. Conversely, the resource distribution in a low cue validity condition exhibits a lower maximum at the cued but more available resources at the uncued location, decreasing the validity effect. The data presented here suggest that nicotine promotes cue uncertainty (Yu and Dayan, 2005), and redistributes the attentional resources in favor of the uncued location in the high cue validity condition. This results in speeded target detection in invalid trials at the cost of target detection in validly cued trials. Thus, the current data provide further evidence that nicotine flattens the distribution of attentional resources in situations where the resource distribution has a strong peak due to top-down modulation.

Neural data

The present study aimed at identifying those brain areas related to attentional reorienting in which neural activity is differentially modulated as a function of cue validity and cortical acetylcholine levels (nicotinic cholinergic stimulation vs. placebo). In accordance with our hypothesis we observed a

nicotine-induced reduction of reorienting-related activity in right parietal brain regions (superior parietal cortex/IPS and TPJ) in invalid trials in the context of high cue validity. Both cortical regions are known to play key roles in attentional processes. The IPS is part of an orienting network responsible for the voluntary control of attention, i.e., for the top-down selection of stimuli (Corbetta and Shulman, 2002). The TPJ region on the other hand is supposed to signal the appearance of unexpected or unattended events to this orienting network (Corbetta and Shulman, 2002) and it has been suggested that this temporo-parietal area is involved in balancing top-down information and bottom-up sensory input (Serences et al, 2005). Thus, the reduced activity of the TPJ and the IPS region under nicotine could be the neural mechanism underlying the behavioral nicotinic effect of a reduced impact of top-down expectations.

Interestingly, while reducing neural activity in invalid trials in the 90% cue validity condition, nicotine increased activity in invalid trials in the 60% cue validity condition in parietal brain areas (superior parietal cortex/IPS, angular gyrus). These results might seem inconsistent with the findings of Giessing et al (2006) showing reduced activity in areas adjacent to the intraparietal sulcus in invalid trials in the context of 64% cue validity. One possible reason for these discrepancies could be the use of two different cues in the present study. Whereas the study by Giessing et al (2006) employed one cue type only (i.e., cue validity was manipulated across different experimental blocks), the task in this study required a matching of cue identity (green, blue) and cue validity (90%, 60%). This could have emphasized the differences between the two experimental conditions, thereby possibly promoting the observed dissociation in the neuromodulatory effects of nicotine in the two cue validity conditions.

How could the pharmacological modulation of parietal brain regions be accomplished? Sarter et al (2005) proposed that the cortical cholinergic fibers emanating from the basal forebrain project to an ‘anterior attention system’ which regulates the activity of posterior brain areas and includes the prefrontal cortex. The present study yielded a cueing x cue validity x drug interaction in the middle frontal gyrus within the right prefrontal cortex and within the left anterior cingulate cortex. It has been suggested that the anterior cingulate and

prefrontal cortex are part of a system involved in effortful cognitive control which is supposed to be mediated by cholinergic neurotransmission (Sarter et al, 2006). However, the question whether the anterior cingulate cortex is only involved in the detection of negative events (like, e.g., errors) or rather represents an instance of control itself remains a matter of debate (Sarter et al, 2006). Thus, the activation observed could on the one hand be linked to the processing of attentional effort related to reorienting attention in the two different cue validity conditions. On the other hand, however, we observed higher response variability in invalid trials in the high cue validity condition under placebo. Hence, provided that the subjects appraised these occasional delays in responding in this experimental condition as deficient performance in the task, the activation of the anterior cingulate cortex could as well be attributed to error detection processes (see, e.g., Menon et al, 2001).

Taken together, our results suggest interaction effects of the pharmacological and cognitive modulations of attentional reorienting which can be observed on both a behavioral as well as a neuronal level.

Disclosure/Conflict of Interest

We declare that, except for income received from the primary employer and grants from the Deutsche Forschungsgemeinschaft (KFO-112, TP 8) to CMT and GRF, no financial support or compensation has been received from any individual or corporate entity over the past three years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest. The placebo chewing gums used in the present study were provided by courtesy of Pharmacia/Pfizer (Helsingborg, Sweden).

Acknowledgements

We are grateful to our colleagues from the MR and Cognitive Neurology groups for valuable support and discussions.

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2.3 Experiment 2

2.3.1 Vossel, S., Weidner, R., Thiel, C.M. & Fink, G.R. (submitted). What is 'odd' in Posner's location-cueing paradigm? Neural responses to unexpected location and feature changes compared

What is 'odd' in Posner's location-cueing paradigm? Neural responses to unexpected location and feature changes compared

Simone Vossel[1,2], Ralph Weidner[1,2], Christiane M. Thiel[3] & Gereon R. Fink[1,2,4]

[1] Institute of Neuroscience and Biophysics - Medicine, Research Centre Jülich, 52425 Jülich, Germany

[2] Brain Imaging Centre West, Research Centre Jülich, 52425 Jülich, Germany

[3] Institute of Biology and Environmental Sciences, University of Oldenburg, 26111 Oldenburg, Germany

[4] Department of Neurology, University Hospital Cologne, 50924 Cologne, Germany

Corresponding author:

Simone Vossel,

Institute of Neuroscience and Biophysics - Medicine, Research Centre Jülich

Leo-Brandt-Str.5, 52425 Jülich, Germany

phone: +49-2461-61-4007, fax: +49-2461-61-2820,

email: s.vossel@fz-juelich.de

Abstract

Within parietal cortex the temporo-parietal junction (TPJ) and the intraparietal sulcus (IPS) seem to be involved in both spatial and non-spatial functions: Both areas are activated when misleading information is provided by invalid spatial cues in Posner's location-cueing paradigm, but also when infrequent deviant stimuli are presented within a series of standard events. In the present study we used functional magnetic resonance imaging (fMRI) to investigate the distinct and shared brain responses to (i) invalidly cued targets requiring attentional reorienting, and (ii) to target stimuli deviating in color and orientation leading to an oddball-like distraction effect. Both unexpected location and feature changes were accompanied by a significant slowing of manual reaction times. Bilateral TPJ and right superior parietal lobe (SPL) activation was observed in response to invalidly as compared to validly cued targets. In contrast, bilateral inferior occipito-temporal cortex, left inferior parietal cortex, right frontal areas and the cerebellum showed stronger activation in response to deviant than to standard targets. Common activations were observed in the right angular gyrus along the IPS and the right inferior frontal gyrus. We conclude that the superior parietal and temporoparietal activations observed here as well as previously in location-cueing paradigms do not merely reflect the detection and processing of unexpected stimuli. Furthermore, our data suggest that the right IPS and inferior frontal gyrus are involved in attentional selection and distractor processing of both spatial and non-spatial features.

Introduction

Human lesion and functional imaging studies suggest that sub-regions of the parietal cortex are involved in covert reorienting of attention in space as well as in the detection of salient unexpected events (for reviews, see Corbetta & Shulman, 2002; Husain & Nachev, 2007). In particular, it has been suggested that the superior parietal lobe (SPL) is activated by spatial attention shifts (e.g., Vandenberghe, Gitelman, Parrish & Mesulam, 2001; Yantis et al., 2002). The cortex adjacent to the intraparietal sulcus (IPS) and the temporo-parietal junction (TPJ) has been implicated in visuospatial attentional reorienting in response to invalid spatial cues (e.g., Arrington, Carr, Mayer & Rao, 2000; Corbetta, Kincade, Ollinger, McAvoy & Shulman, 2000; Thiel, Zilles & Fink, 2004; Giessing, Thiel, Rösler & Fink, 2006; Vossel, Thiel & Fink, 2006). Based upon these observations, it has been suggested that the IPS is involved in top-down attentional control (Hopfinger, Buonocore & Mangun, 2000; Corbetta & Shulman, 2002), while the TPJ is supposed to signal the appearance of unexpected but behaviorally relevant stimuli occurring outside the current focus of attention to an IPS-frontal eye fields (FEF) network (Corbetta & Shulman, 2002). Importantly, however, the TPJ has also been implicated in the detection of deviant stimuli in oddball paradigms even when no spatial reorienting of attention is required (e.g., Linden et al., 1999; Clark, Fannon, Lai, Benson & Bauer, 2000; Downar, Crawley, Mikulis & Davis, 2000, 2001; Bledowski, Prvulovic, Goebel, Zanella & Linden, 2004). Albeit less consistently, activation adjacent to the IPS in response to oddball stimuli has also been reported (Bledowski et al., 2004; Downar et al., 2000, 2001; Marois, Leung & Gore, 2000). Thus, these two subregions of parietal cortex seem to subserve both spatial and non-spatial functions which cannot simply be captured by dorsal versus ventral stream dichotomies (Husain & Nachev, 2007).

Visuospatial attentional reorienting is usually investigated using Posner's location-cueing paradigm (Posner, 1980) in which spatial cues predict the location of behaviorally relevant targets with a certain probability (typically ~ 80% validity in case of centrally presented cues). Subjects respond slower to invalidly as opposed to validly cued targets and the reaction time (RT) difference is used as an indicator for the time needed to reorient attention in

space. Likewise, in the analysis of functional imaging data, invalid trials are contrasted with valid trials to isolate those brain regions differentially involved in the reorienting of attention (Arrington et al., 2000; Corbetta et al., 2000; Thiel et al., 2004; Giessing et al., 2006; Vossel et al., 2006). However, invalid trials differ from valid trials not only with regard to the position of the target stimulus (occurring at the unexpected or the expected location, respectively), but also in the frequency of their occurrence (e.g., 80 vs. 20%) and thus in unexpectedness and saliency. In a previous study (Vossel et al., 2006), we have shown that the proportion of valid to invalid trials (i.e., cue validity) affects reorienting-related activity in the right inferior parietal and temporo-parietal cortex. Activity in these areas was enhanced when subjects had to reorient attention in the context of a high as compared to a low cue validity condition, i.e., when invalid trials were more infrequent and unexpected. Given that deviant stimuli in oddball paradigms elicit activation in similar brain regions, it thus remains to be investigated whether those areas together with those identified in other studies employing location-cueing paradigms indeed reflect spatial reorienting processes per se. Alternatively, those regions could respond to unexpected, infrequent and salient events in general (Corbetta & Shulman, 2002).

Accordingly, the aim of the present functional magnetic resonance imaging (fMRI) study was to dissociate the neural correlates of visuospatial attentional reorienting and non-spatial visual oddball distraction. To address this question, we designed a paradigm in which we orthogonally manipulated the spatial cueing (valid and invalid) and task-irrelevant stimulus properties of the targets (resulting in both standard and infrequently occurring deviant target stimuli).

Since it has been shown that RT costs are likewise observed in location-cueing as well as in visual oddball paradigms when subjects are engaged in a primary task (i.e., in response to task-irrelevant stimulus changes; Meinke, 2006; Meinke, Thiel & Fink, 2006; Berti & Schröger, 2004, 2006), subjects performed a discrimination task in which they had to make spatial frequency judgments of laterally presented target stimuli (sinusoidal gratings). The targets were preceded by spatial cues indicating their location correctly in 80% of the

trials. Importantly, in 80% of all trials the color and orientation of the target were held constant (standard targets), while both features changed in the remaining 20% of the targets (deviant targets). We tested for both distinct and common neural activity in response to changes in location (invalid vs. valid trials) and to changes in orientation and color of the target (deviants vs. standards), respectively.

Methods

Subjects

Twenty-four subjects with no history of neurological or psychiatric disease gave written informed consent to participate in the study. Four subjects were excluded from further analysis due to excessive head movement during fMRI scanning. Therefore, data from twenty subjects were analyzed (9 males, 11 females; age range from 19-38 years; mean age 26.15 years). All subjects were right-handed as indexed by a handedness inventory (Oldfield, 1971). Intact color vision was tested with an adaptation of the Ishihara color tables (Velhagen & Broschmann, 2003).

Stimuli and experimental paradigm

We used a location-cueing paradigm with central predictive cueing (Posner, 1980). The stimuli were shown on a TFT screen behind the MR scanner and were presented to the subjects by means of a mirror-system. Viewing distance was approximately 245 cm. Subjects were presented with two horizontally arranged boxes (1° wide and 4° eccentric in each visual field, see figure 1). A central diamond (0.5° eccentric in each visual field) was placed in between serving as a fixation point. Cues consisted of a 200 ms brightening of one side of the diamond depicting an arrowhead pointing to one of the peripheral boxes. The cue was followed by a target appearing for 100 ms in one of the boxes. To prevent temporal orienting, we used two randomly occurring cue-target intervals (400 and 700 ms). The cues were valid in 80% of the trials. The targets were circular sinusoidal gratings (0.9° eccentricity) with two different spatial frequencies (‘fine’ grating: 7 circles per grating; ‘coarse’ grating: 3 circles per grating). Subjects were asked to report the spatial frequency of the target stimulus as quickly as possible by button presses with the index and middle finger of their right hand. Fine and coarse gratings were presented randomly and with equal probability (i.e., 50%). The gratings could be either in grayscale or in red and green color and were presented with 4 possible orientations (0°,

45°, 90°, 135°). One specific combination of color and orientation (e.g., grayscale grating with 0° orientation, see figure 1) was defined as the 'standard target' which was presented in 80% of the trials. Twenty percent of the targets, however, were 'deviants' in which both the color and the orientation of the gratings changed (e.g., red-green gratings with 45°, 90° and 135° orientation). We varied both stimulus features of the targets in the deviant trials at the same time (i.e., both color and orientations) because this reliably produced RT costs in a behavioral pilot study. Note that these variations were completely irrelevant for the task. Thus, a location-cueing paradigm was combined with a visual oddball paradigm (see figure 1), resulting in a 2x2 design with the factors 'cueing' (valid, invalid) and 'target' (standard, deviant). In addition, approximately 2 % of the experimental trials were 'catch trials' in which the cues were not followed by any targets.

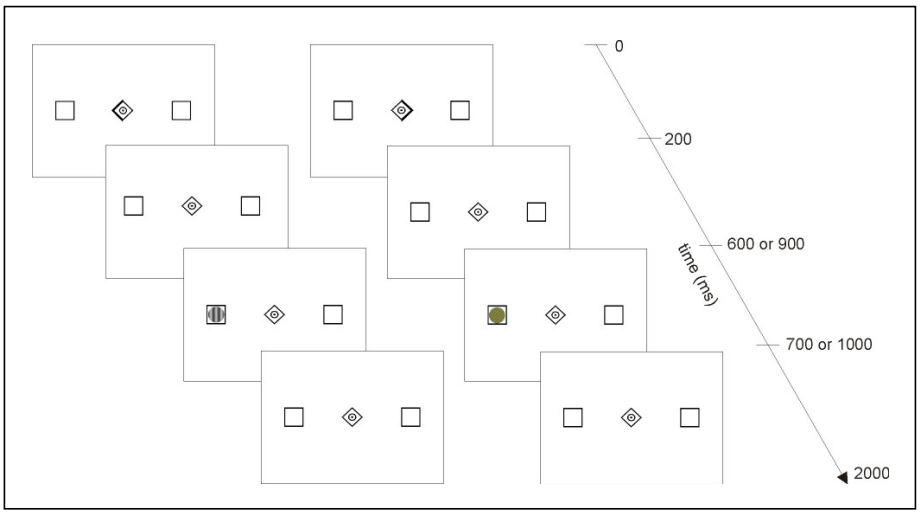

Figure 1. Experimental paradigm. Illustration of an exemplary event sequence during trials with a validly cued standard (grayscale grating, 0° orientation) and an invalidly cued deviant target (red-green grating, 45° orientation). Note that in this example other possible deviants were red-green gratings with 90° and 135° orientation, respectively. The allocation of color and orientation to standards and deviants, respectively, was counterbalanced across subjects. Subjects were asked to fixate the central diamond throughout the experiment and to make spatial frequency judgments of the target stimuli (fine or coarse). The proportion of valid to invalid cues and standard to deviant targets was 4:1.

The allocation of the responding fingers (right index and middle finger) to the two spatial frequencies (fine and coarse) as well as the allocation of color and orientation to standard and deviant targets, respectively, was counterbalanced across subjects. Subjects were informed about the different experimental conditions and completed a short practice session prior to performing the task in the MR scanner. Trials were presented every 2000 ms. The experiment consisted of 959 trials including 320 'null events' (Josephs & Henson, 1999) where a baseline stimulus was displayed, leading effectively to variable stimulus onset asynchronies (SOAs) (i.e., 2000 ms, 4000 ms, 6000 ms, etc.). The duration of the experiment was 34 minutes. The scanning session

included two rest periods of approximately 1 minute during which the word 'pause' was shown on the display and the subjects were allowed to close their eyes. This was done to prevent deterioration of fixation ability due to exertion of the eyes. Restart of the task was indicated by a tone.

Data acquisition

T2*-weighted echoplanar (EPI) images with blood oxygen level-dependent (BOLD) contrast (matrix size 64 x 64, voxel size 3.1 x 3.1 x 3.0 mm^3) were obtained using a 3 T MRI System (Trio, Siemens, Erlangen, Germany). Additional high-resolution anatomical images (voxel size 1 x 1 x 1 mm^3) were acquired using a standard T1-weighted 3D MP-RAGE sequence.

Nine hundred seventeen EPI volumes of thirty-six 3 mm thick axial slices were acquired sequentially with a 0.3 mm gap (repetition time 2.2 s, echo time 30 ms). The first 5 volumes were discarded to allow for T1 equilibration effects. The data were pre-processed and analyzed with Statistic Parametric Mapping software SPM5 (Wellcome Department of Imaging Neuroscience, London; Friston, Holmes, Worsley, Poline, Frith & Frackowiak, 1995; http://www.fil.ion.ucl.ac.uk/spm5.html). To correct for interscan movement, the images were spatially realigned to the first of the remaining 912 volumes and subsequently re-realigned to the mean of all images after the first step. Then, the mean EPI image for each subject was computed and spatially normalized to the MNI single subject template using the 'unified segmentation' function in SPM5. The resulting parameters of a discrete cosine transform, which define the deformation field necessary to move the subjects data into the space of the MNI tissue probability maps were then combined with the deformation field transforming between the latter and the MNI single subject template. The ensuing deformation was subsequently applied to the individual EPI volumes as well as to the T1 scan, which was coregistered to the mean of the realigned EPIs beforehand. All images were hereby transformed into standard stereotaxic space and resampled at 2 x 2 x 2 mm^3 voxel size. The normalized images were spatially smoothed using an 8 mm full-width half-maximum (FWHM) Gaussian

kernel to meet the statistical requirements of the General Linear Model and to compensate for residual macroanatomical variations across subjects.

Statistical analysis of imaging data

Data were analyzed with SPM5 employing a random effects model. Seven regressors were defined at the single-subject level (validly cued standard targets, invalidly cued standard targets, validly cued deviant targets, invalidly cued deviant targets, catch trials, missed/incorrect responses, pauses). The event types were time-locked to the onset of the target by a canonical synthetic hemodynamic response function (hrf) and its first order temporal derivative. The six movement parameters of the realignment (rigid body translation in the x-, y- and z-plane as well as rotation around the x-, y-, and z-axis) were included in the design matrix as additional regressors. Data were scan-wise globally scaled to reduce globally distributed confounding effects (Kiebel & Holmes, 2004) and high-pass filtered at 1/128 Hz. For each subject, 4 contrast images were created for each experimental condition (each trial type vs. baseline) and entered into a 1 x 4 within-subjects ANOVA (flexible factorial design in SPM5 including an additional factor modeling the subject means). Inhomogeneity of variance and correlation of measurement were estimated with a Restricted Maximum Likelihood (ReML) algorithm.

To isolate brain areas involved in the spatial reorienting of attention (i.e., to test for the main effect of the factor cueing) we used a directed t-contrast comparing all invalid to all valid trials. Similarly, brain areas associated with non-spatial visual distraction were identified by contrasting all deviant with all standard trials (i.e., by testing for the main effect of the factor target). Interaction effects between these two factors were tested with two directed t-contrast. Activations are reported at a statistical threshold of $p<.05$ corrected at cluster-level (cluster size estimated at voxel-level at $p<.001$ uncorrected) (Poline, Worsley, Evans & Friston, 1997). To isolate the distinct brain activations in response to spatial reorienting and oddball distraction, respectively, we used a masking procedure in which each main effect contrast ($p<.05$ corrected at cluster-level) was exclusively masked with the other contrast at a low statistical

threshold ($p<.05$ uncorrected for multiple comparisons). Hence, with this procedure, those voxels that reach a level of significance of $p<.05$ (uncorrected) in the mask contrast are excluded from the analysis.

To test for common neural activations we used a conjunction analysis testing for the conjunction null hypothesis (Friston, Penny & Glaser, 2005). As cluster-level inference can validly be applied to single statistic images only and not to image intersections like in a conjunction, we used a threshold of $p<.001$ uncorrected (equivalent to a conjoint $p<1*10^{-6}$) and a cluster threshold of 10 contiguous voxels when reporting the results of this analysis.

Statistical analysis of behavioral data

Reaction times (RTs) faster than 100 ms (i.e., anticipated responses) were excluded from the analysis. Median RTs were calculated for the four experimental conditions in each subject. These median RTs were analyzed with a repeated-measure ANOVA with the factors 'cueing' (valid, invalid) and 'target' (deviant, standard). Omissions and incorrect responses were summed-up and expressed as percentage values. For the 'catch trials' false alarm responses were determined and transformed into percentage values.

Eye movement control

Eye position was monitored during scanning with an MR-compatible infrared eye tracker (SensoMotoric Instruments® SMI, Berlin Germany). Eye movement data were analyzed to assure that the subjects were able to maintain eye fixation in response to the cue and the target stimuli. Therefore, the time interval between cue and target appearance as well as the time period after the appearance of the targets were analyzed. The latter analysis was performed separately for the 4 experimental conditions (i.e., validly and invalidly cued standard targets and validly and invalidly cued deviant targets) to control for differences in fixation performance between the conditions. Analysis was restricted to a time frame of 800 ms after target appearance (note that on average the response occurred within about 600 ms after target appearance).

For both analyses (time interval between cue and target and 800ms time interval after target appearance) the amount of time in which the eye movements stayed within a range of two standard deviations was determined and transformed into a percentage value. As in the analysis of RTs, differences in fixation performance between conditions were tested with a 2x2 repeated-measure ANOVA with the factors ‘cueing’ and ‘target’.

Results

Behavioral Data

None of the subjects showed any anticipated or false alarm responses. Missed and incorrect responses amounted together on average to 3.4 % (± 0.58 SEM). The ANOVA of the median RTs yielded a main effect of the factor 'cueing' ($F(1,19)=24.56$; $p<.001$; $\eta_p^2=.564$), reflecting slower responses to invalidly than to validly cued targets. Moreover, we observed a significant main effect of 'target' ($F(1,19)=95.26$; $p<.001$; $\eta_p^2=.834$) reflecting the RT costs caused by deviant target stimuli. Thus, both invalid cues and deviant targets caused a significant prolongation of RTs. The cueing x target interaction was not significant ($p>.3$) as the average magnitude of RT costs was almost of equal magnitude (RT of all invalid minus RT of all valid trials: mean ± SEM: 28.3 ± 3.8 ms; RT of all deviant minus all standard trials: 34.1 ± 3.4 ms). The means of the median RTs for each experimental condition are depicted in figure 2.

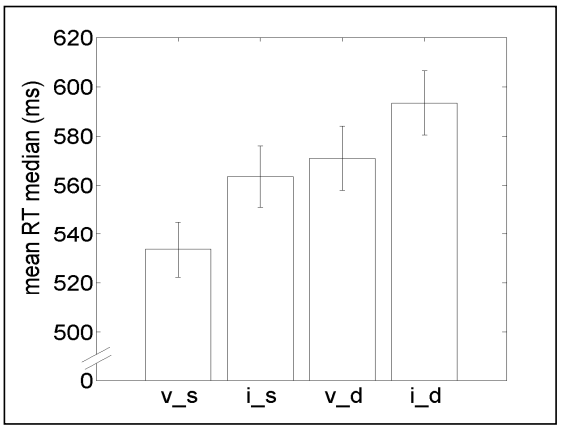

Figure 2. Behavioral Data. Averaged median reaction times (RTs) and standard errors of the mean (SEM) for the four experimental conditions. *v_s*: validly cued standard targets; *i_s*: invalidly cued standard targets; *v_d*: validly cued deviant targets; *i_d*: invalidly cued deviant targets.

Eye movement Data

The subjects spent 94.8 ± 1.0 % (mean ± SEM) of the time between cue and target appearance within a fixation zone of 2 SDs. There were no significant differences in fixation performance after target appearance between the four experimental conditions (validly cued standard targets: 96.0 ± 0.8 %, invalidly cued standard targets: 95.6 ± 0.9 %, validly cued deviant targets: 95.7 ± 0.9 %, invalidly cued deviant targets: 95.6 ± 1.3 %; all p-values of the ANOVA terms >.4).

Neural Data

Visuospatial attentional reorienting

The comparison of all invalid versus all valid trials (i.e., testing for the main effect of cueing to isolate brain regions involved in visuospatial attentional reorienting) yielded activation in the superior and middle temporal gyrus (including parts of the temporo-parietal junction, TPJ) in both hemispheres (voxels of peak activation: x=66, y=-44, z=11, Z=5.17; 774 voxels; x=-58, y=-54, z=13, Z=4.92; 456 voxels). Moreover, we observed activation in the posterior part of the middle temporal gyrus of the right hemisphere (x=44, y=-62, z=13, Z=4.39; 155 voxels) and in the right superior parietal lobe (SPL) (x=18, y=-72, z=57, Z=3.95; 221 voxels) which extended into the intraparietal sulcus (IPS). When masked exclusively with the main effect of target (deviants > standards), all four regions survived the masking procedure (see figure 3 *(red)* and table 1), suggesting that these brain areas were indeed involved in spatial reorienting of attention and not in the detection of infrequent events per se.

Table 1. Distinct and common brain areas involved in visuospatial reorienting of attention and visual oddball distraction.

Region	Side	MNI coordinates			Voxels	Z score
		x	y	z		
[invalid > valid] masked excl. by [deviant > standard]						
superior/middle temporal gyrus, TPJ	R	66	-40	9	655	5.15*
	L	-58	-54	13	413	4.92*
posterior middle temporal gyrus	R	44	-62	13	148	4.39
superior parietal lobe (SPL)	R	20	-72	59	145	3.93
[deviant > standard] masked excl. by [invalid > valid]						
inferior frontal gyrus	R	50	36	17	372	5.42*
insula	R	36	20	-7	132	4.37
inferior parietal lobe (IPL)	L	-42	-36	53	428	4.28
inferior occipito-temporal cortex, fusiform gyrus	L	-50	-62	-15	547	5.60*
	R	50	-58	-17	680	5.44*
cerebellum	L	-30	-36	-27	127	4.79
Conjunction: [invalid > valid] ∩ [deviants > standards]						
inferior frontal gyrus	R	54	12	41	10	3.38
angular gyrus, IPS	R	32	-66	51	21	3.38

*Activations denoted with an asterisk are also significant after applying a family-wise error correction for multiple comparisons at the voxel-level.

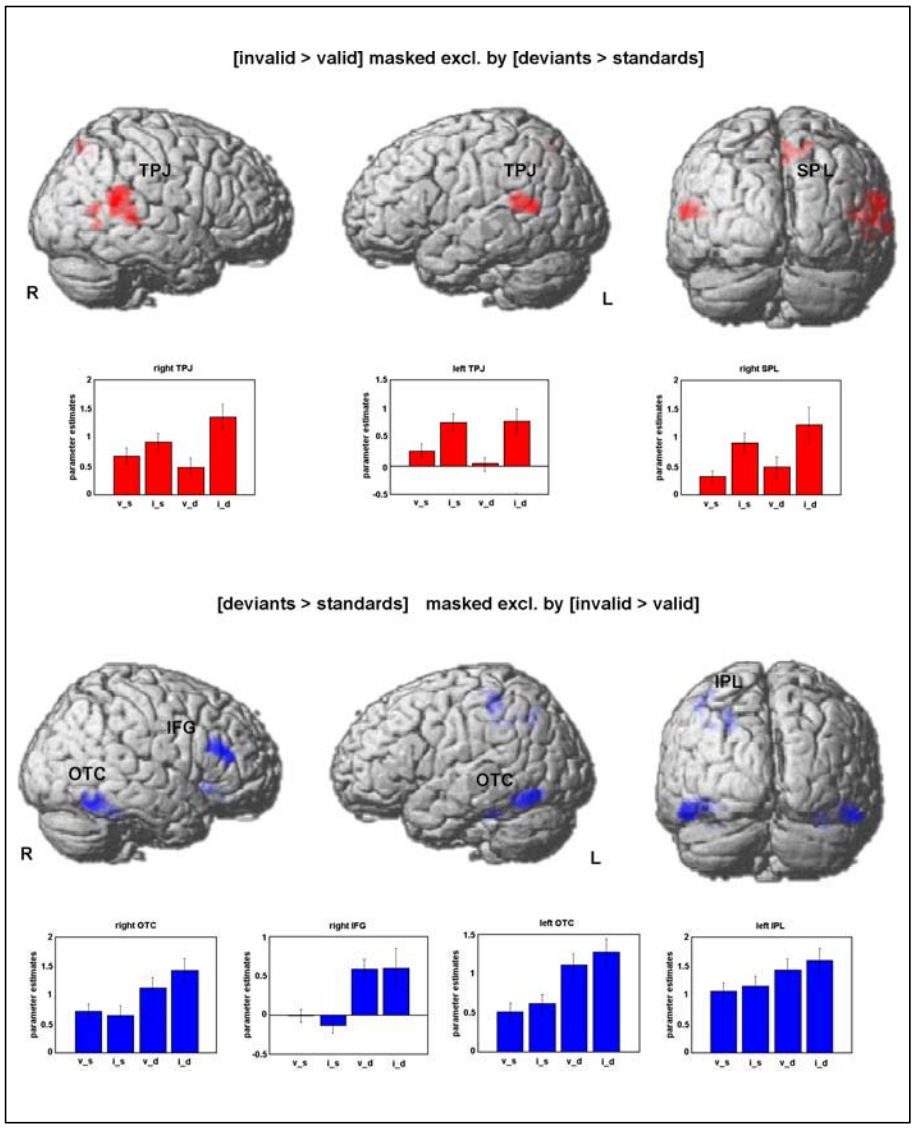

Figure 3. Neural Data. Distinct neural correlates of visuospatial attentional reorienting (red) and visual oddball distraction (blue). *TPJ*: temporo-parietal junction; *SPL*: superior parietal lobe; *IFG*: inferior frontal gyrus; *OTC*: occipito-temporal cortex; *IPL*: inferior parietal lobe. See legend of figure 2 for other abbreviations.

Visual oddball distraction

The contrast of all deviant versus all standard targets (i.e., the main effect of target) resulted in bilateral activation of the inferior temporal gyrus which extended into inferior occipital areas as well as the fusiform gyrus (occipito-temporal cortex, OTC, x=-50, y=-62, z=-15, Z=5.6; 573 voxels; x=50, y=-58, z=-15, Z=5.59; 169 voxels). Furthermore, the right inferior frontal gyrus (x=50, y=36, z=17, Z=5.42; 438 voxels), the right anterior insula (x=36, y=20, z=-7, Z= 4.37; 135 voxels), the right angular gyrus along the IPS (x=30, y=-68, z=39, Z=4.71; 465 voxels), the left inferior parietal lobe (IPL) (x=-42, y=-38, z=53, Z=4.57; 659 voxels) and the left cerebellum (x=-30, y=-36, z=-27, Z=4.79; 127 voxels) showed significantly stronger activation in response to deviant than to standard targets. Only the activation in the right angular gyrus/IPS did not survive the analysis with exclusive masking with the main effect of cueing (see figure 3 *(blue)* and table 1 for results of the masking analysis).

Interaction effects

None of the two interaction contrasts ([invalidly cued standards > validly cued standards] > [invalidly cued deviants > validly cued deviants]; [invalidly cued deviants > invalidly cued standards] > [validly cued deviants > validly cued standards]) revealed any significant activations at cluster-level inference. This suggests that neither the differential activation related to attentional reorienting depended on the type of the target stimulus (standard or deviant) nor was the differential activation elicited by the deviants (versus the standard targets) influenced by the mode of spatial cueing (valid or invalid).

Conjunction analysis

The conjunction analysis testing for common activations of the two main effect contrasts (i.e., for a logical AND) yielded two activation clusters in the right inferior frontal gyrus and in the right angular gyrus adjacent to the IPS (see figure 4 and table 1). As revealed by the BOLD signal changes in the four experimental conditions (see figure 4 for the IPS), these two regions showed

higher activity in trials with invalidly cued standards (location change only) and validly cued deviants (feature change only) when compared to trials with validly cued standards. The activity was highest in trials with invalidly cued deviants (location and feature change).

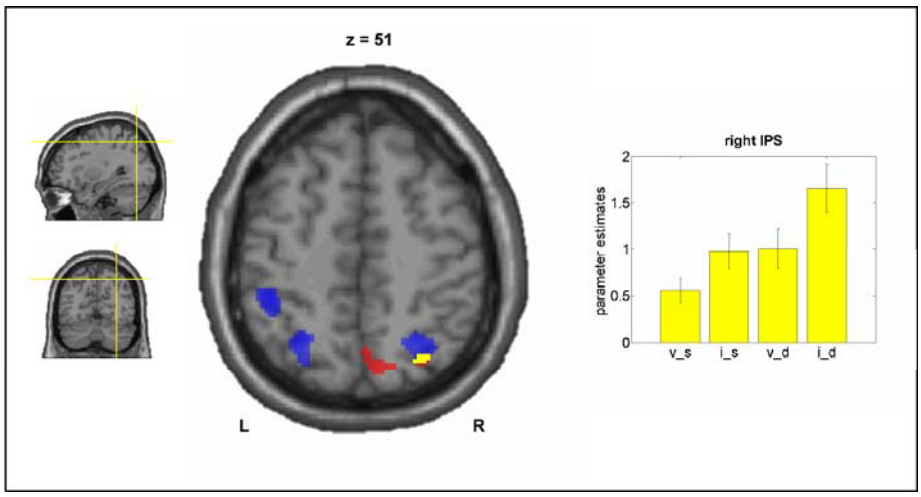

Figure 4. Neural Data. Common neural activation for visuospatial attentional reorienting and visual oddball distraction in parietal cortex. *blue*: main effect of cueing (invalid>valid); *red*: main effect of target (deviants > standards). Note, that here the results without exclusive masking are depicted. *yellow*: results of the conjunction analysis. *IPS:* intraparietal sulcus. See legend of figure 2 for other abbreviations.

Discussion

In this fMRI study we included elements of an oddball paradigm within the context of Posner's location-cueing paradigm in order to dissociate the neural correlates of visuospatial attentional reorienting and visual oddball distraction as well as to reveal shared neural processes. While performing a spatial frequency judgment of a sinusoidal grating, subjects were presented with unexpected changes in the location and/or the color and orientation of the target stimuli. At the behavioral level, both invalid spatial cueing and the occurrence of deviant targets resulted in a significant slowing of RTs. Importantly, both experimental conditions produced RT costs which were equal in magnitude. At the neural level, spatial reorienting of attention was accompanied by activation of bilateral temporo-parietal as well as right superior parietal brain areas. In contrast, bilateral inferior temporal and occipital areas, left inferior parietal and right frontal regions showed stronger activation in response to deviant than to standard targets. A conjunction analysis revealed common activations of the two contrasts in the right inferior frontal gyrus and in the angular gyrus along the IPS. Neither at the behavioral nor at the neural level did we observe significant interaction effects.

Neural data

Temporo-parietal junction (TPJ)

In the present study activation of the TPJ was observed when comparing invalidly and validly cued target stimuli, i.e., in response to unexpected location changes requiring reorienting of attention. Although this activation was found in both hemispheres, it was more pronounced in the TPJ of the right hemisphere. This finding is consistent with other imaging studies investigating the neural mechanisms underlying visuospatial reorienting of attention which either observed right-hemispheric (Arrington et al., 2000; Corbetta et al., 2000; Thiel et al., 2004; Vossel et al., 2006) or bilateral (Giessing et al., 2006; Kincade,

Abrams, Astafiev, Shulman & Corbetta, 2005) activation in this area when contrasting invalid and valid trials in the location-cueing paradigm. Since the TPJ activation in the present study survived the exclusive masking with the contrast comparing the infrequently occurring deviants to the standard targets, it is unlikely that the activation here and in previous studies is caused by the increased unexpectedness of invalid trials per se. The activation in this study moreover overlapped with a region within the TPJ that shows stronger reorienting-related activation when the cue is highly valid and invalid trials thus are presented with a very low frequency (Vossel et al., 2006). The present results therefore provide further support for the hypothesis that the susceptibility of the TPJ to cue validity reflects changes in the effort needed for attentional reorienting as predicted by attentional gradient models (Madden, 1992) rather than the processing of infrequent events in general.

Indeed, the TPJ did not show higher activation in deviant as compared to standard trials. In contrast, bilateral inferior occipito-temporal, left parietal and right frontal areas (including the anterior insula adjacent to the orbitofrontal cortex) were activated by deviant more than by standard targets. These activations are in accord with a recent model of visual object recognition which proposed that the orbitofrontal cortex is involved in the top-down modulation of the activity in occipito-temporal visual areas (Bar et al., 2006). It could be assumed that the activity in these areas was enhanced in deviant trials because the unexpected feature change interfered with the target recognition (coarse or fine) and thus required more top-down control. The missing activation of the TPJ, however, contrasts with other fMRI studies that observed (mostly bilateral) TPJ activation when subjects had to detect infrequently occurring 'odd' events (Linden et al., 1999; Clark et al., 2000; Downar et al., 2001; Bledowski et al., 2004). Note, however, that in these studies the subjects were explicitly instructed to attend to these events and to respond accordingly by different button presses or to silently count the deviant stimuli (Linden et al., 1999). Exceptions to this are two studies in which subjects had to passively view sensory changes (Downar et al., 2000) or in which stimulus changes were presented in both task-relevant and task-irrelevant dimensions (Downar et al., 2001) and the TPJ was activated. However, in the study of Downar et al. (2000)

activation of the TPJ was only observed when analyzing auditory and multimodal stimulus changes, but not in the unimodal contrast capturing the neural response to visual transitions. The findings of this latter analysis of unimodal contrast changes resembled the results of the present study in that fusiform and occipital as well as right superior parietal brain areas were activated. In the second study by Downar et al. (2001) it was observed that one subregion of the TPJ in the supramarginal gyrus showed sensitivity to the relevance of the stimulus changes while another in the superior temporal gyrus did not. However, the task-irrelevant stimulus changes in that study still had a response suppression component resembling go/no-go paradigms (Downar et al., 2001) and thus the results cannot perfectly be compared to the present study.

In contrast to all of the above mentioned studies, the subjects in our study were engaged in a target discrimination task (spatial frequency judgment) in which both the location and the color and orientation of the target were irrelevant with regard to the required response (fine or coarse grating). In other words, both unexpected changes in the location as well as in the color/orientation of the target could be regarded as two different forms of expectation violation or visual distraction and both conditions were accompanied by almost equally high RT costs. Nevertheless, activation of the TPJ (within the superior temporal gyrus) was observed in response to unexpected location changes only. One reason for this result could be that unlike the color and orientation of the target, the location was explicitly cued. Although we presented both valid and standard trials with 80% probability and thus biased the expectation of the subjects with regard to both properties of the target stimulus, visual short term memory (VSTM) load could have been affected differentially. In particular, one could argue that in contrast to the color/orientation of the target, the (cued) location had to be maintained in the subjects' VSTM on a trial-by-trial basis. Indeed, it has been shown that VSTM load impairs the ability of subjects to detect unexpected task-irrelevant sensory changes (i.e., impairs stimulus-driven attention) by suppressing activity in the TPJ (Todd, Fougnie & Marois, 2005). It could thus be speculated that in the present study VSTM load could have suppressed activation of the TPJ for the

feature change (different dimension), but not for the location change (same dimension as in VSTM). Consistent with that, a study by Melcher and Gruber (2006) in which the subjects were engaged in font size judgments of words also found that rarely occurring color oddballs elicited activation of frontal, superior parietal (IPS) and occipito-temporal areas, but not within the TPJ. It still has to be noted, however, that although no activation was elicited in the TPJ, the deviant stimuli produced significant RT costs in both Melcher's and our study.

Our data are furthermore congruent with lesion studies employing the location-cueing paradigm in stroke patients. Here, it has been demonstrated that in particular lesions within the TPJ lead to a deficit in attentional reorienting, as these patients show disproportionate slow RTs when a contralesional target is preceded by an invalid cue (Friedrich, Egly, Rafal & Beck, 1998).

Superior parietal lobe (SPL) and intraparietal sulcus (IPS)

The right SPL showed significant higher activation in response to invalidly as compared to validly cued targets. As in the TPJ, the activation in this area was still present after explicitly masking the contrast with the comparison of deviant and standard targets. This result is consistent with previous studies as it has been shown that superior parietal areas are involved in spatial attention shifts (Vandenberghe et al, 2001; Yantis et al., 2002; Kelley, Serences, Giesbrecht & Yantis, 2007; Molenberghs, Mesulam, Peeters & Vandenberghe, 2007). It could thus be argued that spatial reorienting of attention in the location-cueing paradigm draws on activation of both ventral (TPJ) and dorsal (SPL) parietal areas, and that these activations persist even after subtracting effects evoked by unexpected and infrequently occurring salient stimuli.

Another region in the right parietal cortex adjacent to the IPS showed activation when testing for the common effects of spatial reorienting and visual oddball distraction with a conjunction analysis (see figure 4). This is in line with the finding that the IPS is involved in both spatial and non-spatial attentional processes (Coull & Frith, 1998). The IPS activation overlapped with an area that has recently been attributed to the recalibration of attentional weights of an

attentional priority map (Molenberghs et al., 2007). Thus, it could be speculated that the changes in location and color/orientation of the target stimulus in the present study required an appraisal of task relevance and accordingly a readjustment of attentional weights. Resembling our results, Molenberghs and colleagues also reported dissociations between the functions of SPL and of a more inferior region adjacent to the IPS. While the SPL generally responded to spatial shifts of attention, the IPS was activated by feature changes even when no spatial shift was required (see also Weidner, Pollmann, Müller & von Cramon, 2002). Other studies showed activation of the IPS elicited by distractor stimuli in three stimulus oddball paradigms (i.e., including standards, distractors and behaviorally relevant targets, Bledowski et al., 2004) or by irrelevant stimuli occurring in the opposite peripheral visual field (Vandenberghe et al., 2005). Moreover, a recent study by Geng, Eger, Ruff, Kristjánsson, Rotshtein and Driver (2006) demonstrated that the IPS is involved in the on-line attentional selection of competing visual stimuli. Therefore, the IPS seems to be involved in selecting task-relevant stimulus features as well as in isolating these features from potential distractions, may they be spatial or non-spatial. Applied to the present study, the IPS activation could thus reflect the refocusing of attention on the spatial frequency of the grating which is particularly required in case of invalidly cued targets and deviant targets.

It should furthermore be noted that we observed coexistent activation in the right inferior frontal gyrus within the prefrontal cortex when contrasting deviant and standard targets as well as in the conjunction analysis. The prefrontal cortex has been shown to be responsible for maintaining goal-relevant information as well as for the control of distractibility (for a review, see e.g., Miller, 2000) and it has been proposed that this region accordingly transmits bias signals to other brain systems (like, probably, the IPS).

Conclusion

In sum, our data show that neural activation related to visuospatial attentional reorienting as assessed with the location-cueing paradigm (invalid > valid trials) is not congruent with neural responses to deviant as compared to standard stimuli and thus cannot only be attributed to the processing of unexpected salient stimuli per se. Only the right IPS and inferior frontal gyrus seem to subserve both spatial attentional reorienting and non-spatial visual distraction processes.

Acknowledgements

We are grateful to our colleagues from the MR and Cognitive Neurology groups for valuable support and discussions. In particular, we thank Marcus Wilms and Shahram Mirzazade for enabling eye tracking in the MR scanner and Simon Eickhoff for his helpful methodological support.

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2.4 Experiment 3

2.4.1 Vossel, S., Kukolja, J., Thimm, M., Thiel, C.M. & Fink, G.R. (in prep.). Nicotinic modulation of visuospatial attention in patients with chronic spatial neglect.

Nicotinic modulation of visuospatial attention in patients with chronic spatial neglect

Short title: Nicotine and spatial neglect

Simone Vossel[1,2], Juraj Kukolja[1,2], Markus Thimm[1,3], Christiane M. Thiel[1,2,4], Gereon R. Fink[1,2,5]

[1] Institute of Neuroscience and Biophysics - Medicine, Research Centre Jülich, 52425 Jülich, Germany

[2] Brain Imaging Centre West, Research Centre Jülich, 52425 Jülich, Germany

[3] Department of Neurology, University Hospital Aachen, 52074 Aachen, Germany

[4] Institute of Biology and Environmental Sciences, University of Oldenburg, 26111 Oldenburg, Germany

[5] Department of Neurology, University Hospital Cologne, 50924 Cologne, Germany

Corresponding author:

Simone Vossel

Institute of Neuroscience and Biophysics – Medicine

Research Centre Jülich

Leo-Brandt-Str. 5, 52425 Jülich, Germany

phone: +49-2461-61-4007, fax: +49-2461-2820, email: s.vossel@fz-juelich.de

Abstract

The deficit to disengage attention from the ipsilesional side of space and to reorient the attentional focus to contralesional stimuli is one key feature of the spatial neglect syndrome. Previous animal and human studies suggest that reorienting of visuospatial attention is modulated by the cholinergic neurotransmitter system. We investigated whether acute cholinergic stimulation via nicotine can facilitate attentional reorienting in patients suffering from chronic spatial neglect. Eight patients with stable spatial neglect symptoms were investigated in a within-subject cross-over design. We employed a location-cueing paradigm and analysed reaction time (RT) differences between validly and invalidly cued targets (i.e., the 'validity effect') as a function of hemifield and session (nicotine/placebo). Nicotine decreased the validity effect for left targets in the location-cueing task in four of the eight patients. Whereas the lesion hardly affected parietal and temporal brain areas in these 'responders', parietal areas were heavily damaged in the 'non-responding' patients. We conclude that in patients with chronic spatial neglect the performance in location-cueing paradigms can be improved by a cholinergic stimulant and that this effect depends on the integrity of the right temporo-parietal cortex.

Keywords

location-cueing paradigm; cholinergic neurotransmission; neuropharmacology

Introduction

Spatial neglect constitutes a complex neurological syndrome caused by focal cerebral lesions in which patients fail to attend to, respond adequately to or orient voluntarily to stimuli in contralesional space (Heilman, Valenstein, & Watson, 2000; Mesulam, 1999; Posner, Walker, Friedrich, & Rafal, 1984; Fink & Heide, 2004). Importantly, neglect symptoms complicate the rehabilitation process (Halligan & Cockburn, 1993) and predict poor recovery of function in stroke patients (Robertson & Halligan, 1999; Cherney, Halper, Kwasnica, Harvey, & Zhang, 2001). Although different mechanisms are likely to underlie the manifold manifestations of neglect, deficits in visuospatial attention play a critical role in the majority of patients. It has been suggested that a specific impairment in disengaging attention considerably contributes to the spatial neglect syndrome: In location-cueing paradigms, patients with right parietal lesions show disproportionate slow reaction times (RTs) when targets on the contralesional side are preceded by an invalid cue (Posner et al., 1984), i.e., when attention has to be disengaged from a location on the intact (ipsilesional) side of space. Accordingly, the reaction time pattern of these patients is characterized by a higher magnitude of the contralesional 'validity effect' (RT difference between invalidly and validly cued targets) which is regarded as an indicator for the costs of attentional reorienting (Posner, 1980). Interestingly, the disengagement deficit correlates with the severity of neglect and recovery from the disengagement deficit parallels the clinical recovery of neglect (Morrow & Ratcliff, 1988).

The treatment of neglect usually involves neuropsychological training (Kerkhoff, 2003; Robertson, Tegner, Tham, Lo, & Nimmo-Smith, 1995; Sturm et al., 2004; Thimm, Fink, Küst, Karbe, & Sturm, 2006). The amelioration of neglect has also been reported after psychophysiological stimulation methods such as neck muscle vibration (Schindler, Kerkhoff, & Karnath, 2002). Unfortunately, most of these strategies have short-term beneficial effects only. Very few controlled studies have investigated the effects of pharmacological challenges in neglect patients. Beneficial (Geminiani, Bottini, & Sterzi, 1998; Mukand et al., 2001) as well as adverse effects (Barrett, Crucian, Schwartz, &

Heilman, 1999; Grujic et al., 1998) were reported after stimulation of the dopaminergic neurotransmitter system. With regard to the noradrenergic system, a recent study (Malhotra, Parton, Greenwood, & Husain, 2006) in three neglect patients suggests that neglect symptoms may be ameliorated by the administration of the noradrenergic agonist guanfacine. According to the neurochemical model of Posner and Fan (2004) the dopaminergic system is primarily associated with executive attentional functions while the noradrenergic system is involved in maintaining sustained attention. In contrast, reorienting of attention is supposed to be mediated by the cholinergic neurotransmitter system which can be stimulated, for example, via the administration of nicotine. Pharmacological studies in animals as well as in humans support this assumption by showing a specific decrease in reaction times to invalidly cued targets associated with a diminished validity effect in location-cueing paradigms after cholinergic stimulation (Murphy & Klein, 1998; Steward, Burke, & Marrocco, 2001; Phillips, McAlonan, Robb, & Brown, 2000; Thiel, Zilles, & Fink, 2005; Witte, Davidson, & Marrocco, 1997; see however Griesar, Zajdel, & Oken, 2002). Importantly, there is evidence that this nicotinic modulation depends on the baseline size of the validity effect (Thiel et al., 2005; see also Newhouse, Potter, & Singh, 2004 for baseline-dependent nicotinic effects). This implies that in particular those subjects that are slow in attentional reorienting (like, e.g., spatial neglect patients) should benefit from cholinergic stimulation.

Attentional processes are mediated by a fronto-parietal cortical network and it is well documented that the forebrain cholinergic fibres projecting to the cortex constitute ‘an integral and necessary component of these networks’ (Sarter & Parikh, 2005, p. 48; for a review see also Sarter, Hasselmo, Bruno, & Givens, 2005). Along these lines, a neglect-like reaction time pattern in the location-cueing paradigm can be induced by a disruption of the cholinergic input to the cortex in animals (Bushnell, Chiba, & Oshiro, 1998). Moreover, functional imaging studies have shown that the nicotinic modulation of attentional functions is associated with altered neural activity in parietal cortex (Lawrence, Ross, & Stein, 2002; Thiel et al., 2005; Giessing, Thiel, Rösler, & Fink, 2006).

Given the slow reorienting of attention towards left-sided targets in neglect patients as well as the theoretical and empirical evidence for attentional reorienting to be facilitated by increased cholinergic neurotransmission, we hypothesized that neglect patients should benefit from nicotinic stimulation. To address this issue we employed a within-subject cross-over design assuming that in a location-cueing paradigm the validity effects for left- and right-sided target stimuli would be reduced in response to nicotine. Because of baseline-dependent pharmacological effects (Thiel et al., 2005, Newhouse et al., 2004), we expected that this reduction would especially be observed for left-sided targets. Taking into account that nicotine modulates parietal cortex activity in healthy subjects, we assumed that the drug effect might depend on the lesion sites of the patients.

Methods

Participants

Eight patients with right-hemispheric lesions of vascular aetiology gave written informed consent to participate in the study (see table 1). To ensure the stability of neglect symptoms over time we exclusively examined patients with chronic spatial neglect, i.e., neglect symptoms persisting at least for 6 months after stroke. To avoid confounding effects with withdrawal from nicotine all patients had to be non-smoking since at least two years. No patient with instable diseases of the heart or the cardiovascular system, diseases of the liver or the gastrointestinal tract, instable diseases of the respiratory organs, psychiatric diseases, or myasthenia gravis was included since these conditions were regarded as contraindications for nicotine administration. Ethics approval was obtained from the local ethics committee.

We employed a battery of paper-and-pencil tests (line cancellation, line bisection, star cancellation, text reading, copying of a star, a cube, a flower, and drawing of a clock) derived from the 'Neglect Test' (NET; Fels & Geissner, 1997; German adaptation of the Behavioural Inattention Test; Wilson, Cockburn, & Halligan, 1987), the 'neglect subtest' of an attention test battery ('Testbatterie zur Aufmerksamkeitsprüfung' TAP; Zimmermann & Fimm, 1992) and a visual search paradigm (a modified version of the 'visual scanning' subtest of the TAP) for the assessment of neglect symptoms. All patients were known to suffer from persisting neglect symptoms because of their participation in prior studies in our lab. Nevertheless, patients were only included in the present study if they showed signs of neglect in at least two of the above mentioned tasks in the placebo session (see table 1).

Table 1. Descriptive data, clinical symptoms, order of drug administration and neuropsychological profile of the included patients.

Patient	**JG**	**UF**	**FK**	**LH**	**WK**	**DG**	**WR**	**JR**
sex	♂	♀	♂	♂	♂	♂	♂	♂
age *(years)*	72	76	74	44	74	62	77	69
time postinjury *(months)*	8	14	20	26	25	36	22	23
left visual extinction	-	+	-	+	+	-	-	-
visual field deficit	-	+ (SQ)	-	-	+ (IQ)	+ (H)	-	-
order of drug administration	p-n	p-n	n-p	n-p	p-n	n-p	n-p	p-n
line cancellation	-	-	-	-	-	-	-	-
line bisection	**+**	**+**	**+**	-	-	**+**	-	-
star cancellation	-	-	**+**	**+**	-	-	-	-
reading	-	**+**	-	**+**	**+**	-	-	-
copying of figures	-	-	**+**	-	-	**+**	**+**	-
clock drawing	-	-	**+**	**+**	-	**+**	-	**+**
TAP *(RT)*	**+**	**+**	-	**+**	**+**	-	**+**	**+**
TAP *(omissions)*	-	**+**	**+**	**+**	**+**	-	**+**	**+**
visual search	**+**	**+**	**+**	-	-	-	**+**	-

H: left hemianopia; IQ: inferior left quadrantanopia; SQ: superior left quadrantanopia; p: placebo; n: nicotine. For the neuropsychological tests neglect-specific behaviour (i.e., rightward bias, leftward omissions or slowing of RT) is depicted with a plus sign printed in bold.

Location-cueing paradigm

We used a location-cueing paradigm with central predictive cueing (Posner, 1980). Subjects were presented with two horizontally arranged boxes (approximately 2.2° wide and 7.2° eccentric in each visual field). A central diamond (1.1° eccentric in each visual field) was placed in between serving as a fixation point. Cues consisted of a brightening of one side of the diamond depicting an arrowhead pointing to one of the two peripheral boxes. The cue stayed on the display for 500 or 800 ms and was immediately followed by the target appearing for 2500 ms in one of the two lateral boxes. Subjects were asked to respond as quickly as possible to the target by a button press with the index finger of their right hand. A trial always ended 4300 ms after cue onset.

We used 5 different cue conditions: valid cues (correctly indicating the location of the upcoming target in 80% of the cases), invalid cues, neutral cues (i.e., not providing any spatial information), 'no cue' trials and catch trials (cues not followed by any target). Trials were presented randomly with variable stimulus onset asynchronies (SOAs). Prior to testing the patients were informed about the different cue conditions and completed a short practice block. Individual median reaction times were calculated for each trial type and each side of space separately. Reaction times faster than 150 ms and longer than 3500 ms were discarded from the analysis. Missed responses were recorded for all target stimuli as well as for left and right targets separately and transformed into percentage scores.

Drug administration

Each patient was tested in two experimental sessions which were separated by one week. Testing always took place on the same time of the day. The order of drug administration was counterbalanced over subjects (see table 1). In each session the patients received either a nicotine polacrilex gum (Nicorette® 2mg, Pharmacia/Pfizer) or a placebo gum with matched taste (Pharmacia/Pfizer) and chewed it for 35 minutes at a rate of approximately one chew all 3 seconds. Drug administration was double-blinded with the exception of the cases WK and WR in which the investigators but not the patients were

informed about the drug condition. Prior to drug/placebo administration all patients were physically examined by an experienced clinician (JK). Twenty minutes after the application of the chewing gum the patients completed a symptom checklist asking for possible adverse side effects. Heart rate and blood pressure were recorded before and 25 minutes after the administration of the chewing gum and blood samples were taken approximately 30 minutes after drug/placebo administration. Blood nicotine levels were determined after liquid-liquid-extraction using an isocratic high performance liquid chromatography (HPLC) with a reversed phase microbore column followed by UV detection. Testing began with the location-cueing paradigm followed by the visual search task, the TAP neglect test and the paper-and-pencil tests. At the end of the second session the patients were asked if they were able to indicate in which session they had received the nicotine or placebo gum, respectively.

Data analysis

Comparisons of the data from the placebo and the nicotine session are reported for the location-cueing paradigm, the visual search task and the TAP neglect test. As the paper-and-pencil tests were administered at the end of each session when a sufficient level of nicotine could no longer be assured, these data were only used for the assessment of neglect symptoms in the placebo session, but not for the assessment of drug effects. Inferential statistics were calculated for the analyses focusing on the whole group of eight patients, but not for any further analyses of subgroups of patients. Due to the small sample size we used nonparametric tests for dependent samples (Wilcoxon signed-ranks test) to test our hypotheses where appropriate. Data are reported at a significance level of $p<.05$ (1-tailed exact significance for directed hypotheses).

Lesion mapping

Structural MRI scans were obtained for all eight patients. Using MRIcro software (http://sph.sc.edu/comd/rorden/mricro.html) lesions were delineated by hand on every single slice of the individual MRI scan and three-dimensional

regions of interest (ROIs) were created. To improve subsequent normalization the MRI scans were segmented into images of grey matter, white matter and cerebrospinal fluid using Statistic Parametric Mapping software SPM2 (Wellcome Department of Imaging Neuroscience, London, http://www.fil.ion.ucl.ac.uk/spm2.html). The MRI scans and ROIs were normalized with SPM2 to the grey matter image of the MRIcro template using the smoothed ROI as a mask to avoid distortions due to the damaged brain tissue (Brett, Leff, Rorden, & Ashburner, 2001). To find areas of lesion overlap across the neglect patients the normalized ROIs were superimposed upon the MRIcro template. For the comparison of subgroups of patients a χ^2-test of the ROIs was conducted using MRIcro.

Results

Physiological and subjective measures

There were no significant differences in heart rate or blood pressure after the administration of the nicotine and the placebo gum, respectively. Blood nicotine levels amounted on average to 3.8 ± 0.56 ng/ml before the start of the experimental tasks in the nicotine session. The data of one sample of the nicotine session was lost due to technical problems. In the placebo session, the level of nicotine was below the limit of quantification (<1 ng/ml) in all samples.

None of the patients reported performance-interfering side-effects (like, e.g., nausea, headache or dizziness) after the administration of the nicotine or the placebo gum, respectively. Three of the eight patients (UF, FK, DG) could not indicate in which session they had received the nicotine or the placebo gum. Four patients (LH, WK, WR, JR) reported flavour differences between the two gums and were able to indicate the nicotine session correctly by comparing the two experimental sessions retrospectively. One patient (JG, a former pharmacist) was able to correctly identify the nicotine and the placebo gum prior to testing.

Location-cueing paradigm

The patients missed 11.2 ± 4.8 % of all targets in the placebo session (11.7 ± 5.1 % of the left and 10.8 ± 4.8 % of the right targets). In the nicotine session there were 6.4 ± 2.6% missed responses overall (7.4 ± 2.9 % for left and 5.4 ± 2.3 % for right targets). The difference between overall missed responses in the placebo and the nicotine session was significant ($Z=-1.78$; $p<.05$). In both sessions false alarm responses to catch trials amounted to 8.7 % (SEM: placebo 4.8; nicotine: 5.8). The patients showed 1.0 ± 0.5 % and 1.7 ± 0.6 % anticipated responses (RTs faster than 150ms) in the placebo and nicotine session, respectively. RTs for the placebo and the nicotine session are summarized in table 2. As expected, the patients responded significantly slower to invalid as compared to valid trials in the placebo session as well as in the

nicotine session (placebo session: left targets: Z=-2.5; p<.001; right targets: Z=-2.1; p<.05; nicotine session: left targets: Z=-2.2; p<.05; right targets: Z=-2.1; p<.05).

Table 2. Averaged median reaction times (in ms) in the different experimental conditions and pharmacological sessions. Standard errors of the mean are shown in parenthesis. P: placebo; N: nicotine.

	left targets					right targets				
	valid cue	**invalid cue**	**neutral cue**	**no cue**	**validity effect**	**valid cue**	**invalid cue**	**neutral cue**	**no cue**	**validity effect**
P	615.2	817.1	698.9	839.0	**201.9**	555.9	671.3	557.4	736.0	**115.4**
	(91.8)	(126.4)	(103.0)	(106.98)	**(55.1)**	(95.8)	(117.23)	(80.9)	(90.8)	**(39.8)**
N	594.9	765.3	640.6	836.5	**170.4**	506.1	581.7	530.4	710.3	**75.6**
	(84.1)	(124.2)	(74.9)	(104.9)	**(71.8)**	(70.1)	(77.8)	(66.5)	(80.9)	**(27.0)**

These RT differences reflect the 'validity effect' (see table 2). The magnitude of the validity effect was higher for left- than for right-sided targets, although this difference did not reach significance neither in the placebo nor the nicotine session (p=.098 for placebo, p=.191 for nicotine session). Significant RT differences between left and right targets were, however, found for all trials types (all p values < .05) except for no cue trials in the placebo session. On average, the validity effects for left- and right-sided targets decreased in response to nicotine. However, this effect did not reach significance and it was actually observable in only four of the eight patients (JG, UF, FK and WR). To elucidate the origin of these discrepancies in response to nicotine we superimposed the lesions for those patients whose validity effect for left targets was reduced in the nicotine session and those whose validity effect stayed constant or even increased in response to nicotine separately (see figure 1 for the behavioural data of the two subgroups). The lesioned brain areas of the responding and non-responding group were compared with a χ^2-test. Results of this analysis are depicted in figure 2. In those patients whose validity effect to left targets was reduced after nicotine administration the parietal cortex was

only scarcely affected or even completely spared by the lesion (see figure 2 A). Moreover, superior temporal brain regions were significantly less affected by the lesions in this patient group. Conversely, parietal and temporal brain areas were extensively damaged in the remaining four patients (see figure 2 B and C) suggesting a dependency of the pharmacological effect of nicotine on the site of the lesion. To substantiate this relationship, we classified the patients' lesions according to temporo-parietal cortex involvement (lesioned vs. spared) and calculated a point-biserial correlation coefficient between this dichotomous variable and the validity effect reduction for left-sided targets in response to nicotine. This yielded a significant correlation for left-sided (r_{pb} = .73; t(6) = 2.63; p<.05) but not for right-sided target stimuli (r_{pb} = .51; t(6) = 1.56; n.s.).

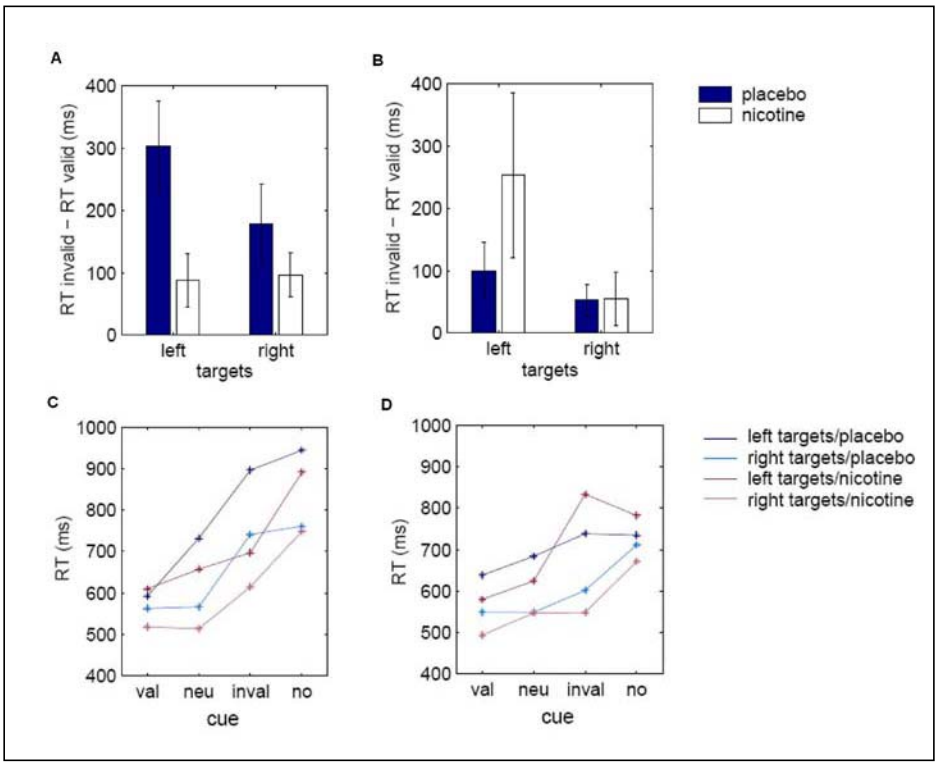

Figure 1. Behavioural data of the 2 patient groups. Validity effects and reaction times (RTs) for the different cue conditions for left and right targets of the 'responding' (A and C) and 'non-responding' patients (B and D). *val:* valid trials; *inval:* invalid trials; *neu:* neutral trials; *no:* no cue trials.

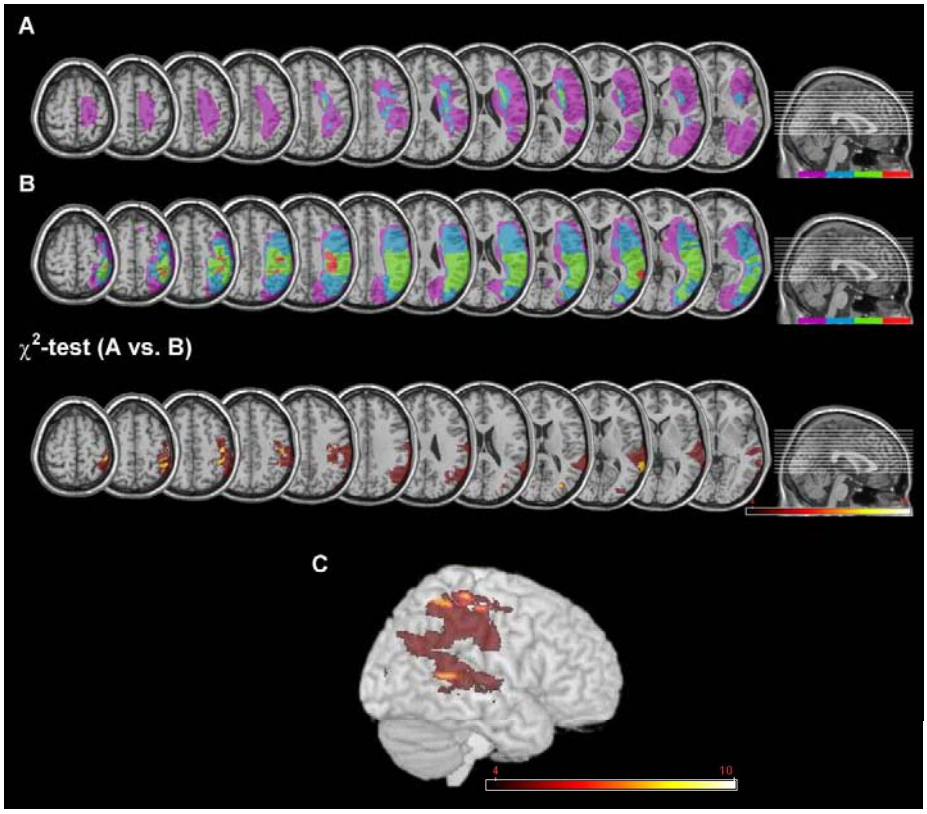

Figure 2. A and B) Lesion overlap for responding and non-responding patients. The contrast image (A vs. B) was thresholded at χ^2 = 3.841 (p<.05) and smoothed in SPM2 with a Gaussian kernel of 2 mm full-width half-maximum. C) 3D-rendering of the smoothed contrast image on the MRIcro template brain.

Visual search paradigm

In the placebo as well as in the nicotine session, the neglect patients significantly detected less target stimuli on the left than on the right side of space (placebo: 40 ± 11.3 % of left targets; 64.3 ± 4.6 % of right targets; Z=-1.9; p<.05; nicotine: 53.7 ± 11.0 % of left target; 72.5 ± 11.0 % of right targets; Z=-1.7; p<.05). There was tendency towards improved target detection for left-sided stimuli under nicotine (p=.094). No consistent differences in response to

nicotine were observed between the two patient groups described in the previous section.

TAP subtest 'neglect'

Median RTs amounted to 1190.9 ± 176.5 ms and 926.4 ± 144.6 ms for left and right targets, respectively, in the placebo session and 1168.8 ± 123.9 ms and 810.1 ± 74.6 ms in the nicotine session. The patients missed 5.7 ± 1.7 out of 22 targets on the left and 2.1 ± 1.0 targets on the right side of space under placebo and 4.5 ± 1.0 left and 2.1 ± 0.8 right targets in the nicotine session. No significant differences between the two experimental sessions were observed and no consistent differences in response to nicotine were found between the two subgroups of patients.

Discussion

In the present study we investigated the effect of an acute nicotine challenge on covert visuospatial attention in eight patients with chronic spatial neglect resulting from right-hemisphere damage. To assess the pharmacological modulation, we used the 'validity effect' (RT difference between invalidly and validly cued targets in a location-cueing paradigm) because a nicotine-induced decrease in this behavioural measure of attentional reorienting is well documented by several animal and human studies. Moreover, there is evidence for a relationship between slow attentional reorienting and clinical signs of neglect (Morrow & Ratcliff, 1988). To our knowledge this is the first study addressing the attentional effect of a cholinergic challenge in this patient group. As hypothesized, nicotine reduced the number of missed targets in the location-cueing paradigm and a similar tendency was observed in a standard neuropsychological visual search test. In four patients the validity effects for left targets in the location-cueing paradigm were markedly reduced in response to nicotine, indicating facilitated reorienting towards the neglected hemifield. However, this effect was not observed in the other four patients. Interestingly, lesion analyses revealed stronger damage to parietal and temporal brain areas in this 'non-responding' patient group. Our data thus suggest that attentional functions can be improved pharmacologically in patients with chronic spatial neglect but that these effects depend on the integrity of temporo-parietal brain regions.

Placebo session

Under placebo the neglect patients in the present study exhibited the expected RT pattern in the location-cueing task (Posner, 1980). They showed faster RTs to validly than to invalidly cued targets in both hemifields. RTs to neutrally cued left-sided targets were intermediate to validly and invalidly cued targets, corroborating that the patients used the spatial cue for allocating their attention. For right-sided targets, however, there was nearly no difference in RTs between validly and neutrally cued targets. Importantly, RTs were slower for left than for right-sided targets. This effect was numerically stronger for

invalidly cued left targets, reflecting the known difficulty of spatial neglect patients in disengaging the attentional focus from the intact side of space (Posner et al., 1984).

Influence of nicotine on target detection and the validity effect

The overall number of missed targets was reduced in response to nicotine in the location-cueing paradigm. A similar tendency of increased target detection rates was evident in the visual search paradigm where in particular more left-sided targets were detected after nicotine administration. The mean validity effect for left- and right-sided targets decreased in response to nicotine, but the reduction of the validity effect for left-sided targets was present in only half of the participating patients. This observation could not be explained by the order of drug administration. We therefore performed a lesion analysis since the effect of nicotine on attentional functions has been ascribed to parietal cortex based on both animal studies (Beane, Drew, Massey, & Marrocco, 2002) and human functional imaging studies (Lawrence et al., 2002; Thiel et al., 2005; Giessing et al., 2006). Strongly supporting these findings, the lesion analysis revealed that parietal as well as temporal brain areas were less affected in those patients who responded to nicotine. Thus, our data indicate that the neuropharmacological effect of nicotine in stroke patients depends on the integrity of those brain areas (or at least parts thereof) where nicotine has been shown to modulate neural activity related to attentional reorienting in healthy subjects. Note, however, that this modulation may originate from remote brain areas: neuronal nicotinic receptors in humans are scarcely located in parietal cortex, but mostly found in thalamic regions, the forebrain and sensorimotor areas (Gotti & Clementi, 2004; Zilles, Schleicher, Palomero-Gallagher, & Amunts, 2002).

Further evidence for the dependency of pharmacological effects on the site of the lesion in neglect patients is provided by the work of Malhotra and coworkers (2006). As discussed by the authors, in that study two out of three patients showed improved exploration of contralesional space after the administration of guanfacine which is supposed to act on the noradrenergic $\alpha 2_A$-

receptors in dorsolateral prefrontal cortex (DLPFC). In contrast to the third patient whose performance did not change after drug administration, prefrontal brain structures were spared by the lesion in these two responding patients.

Alternative explanations

In the present study, several alternative explanations can, at least in principle, account for the observed pharmacological effects. As responding and non-responding patients differed not only with regard to their lesion sites but also in their baseline performance in the location-cueing task (see figure 1), the results could also reflect baseline-dependent rather than lesion-dependent pharmacological effects. This issue cannot be resolved by the present study. Nevertheless, even a baseline-dependency would imply that nicotine has beneficial effects in those patients who are initially slow in reorienting their attention towards contralesional space.

Furthermore, we cannot entirely rule out that nicotine affected cognitive processes other than attentional reorienting. As RTs on average decreased in all cue conditions and the patients missed fewer targets in response to nicotine, the observed effects could also be attributed to improved alertness or sustained attention. In the group of the four responding patients, however, the RT reduction was considerably higher for invalidly cued targets suggesting a differential modulation of reorienting processes. In the remaining four patients, RTs on average were reduced under nicotine in all trial types except for left invalidly cued and left 'no cue' targets (see figure 1 D). Since attention is engaged at the location opposite to target location in invalid trials and at the fixation point in no cue trials, both conditions share the common feature that the targets appear outside the current focus of attention. It has been shown that nicotine particularly influences parietal cortex activity in these two trial types (Thiel et al., 2005). In sum, one could argue that nicotine may influence both spatial reorienting and alertness processes with spatial reorienting only being affected by nicotine in patients without extensive parietal brain damage. Possibly, the influences on alertness are caused by remote effects of nicotine on other neurotransmitter systems. Evidence from microdialysis suggests that

nicotine as well affects noradrenergic, dopaminergic and serotonergic neurotransmission in various brain regions (Singer, Rossi, Verzosa, Hashim, Lonow, & Cooper, 2004). This notion could also explain the results in the visual search paradigm in the present study. Target detection was improved in response to nicotine and this effect was equally observed for left- and right-sided targets in patients with extensive parietal lesions who did not show a reduced validity effect in the location-cueing paradigm under nicotine. In this context it is noteworthy that an interaction of the alerting system (supposed to be mediated by noradrenaline) with the spatial orienting system (supposed to be mediated by acetylcholine) has been postulated on behavioural grounds (Robertson, Mattingley, Rorden, & Driver, 1998) and consistent with that claim amelioration of neglect has been shown subsequent to alertness training (Robertson et al., 1995; Thimm et al., 2006).

Regarding future prospects, more research and larger patient samples are needed to identify the behavioural and anatomical predictors of pharmacological effects in neglect patients. Moreover, longitudinal studies employing chronic treatments are necessary to investigate the stability of the pharmacological effects. Importantly, however, the current data suggest that attentional deficits in chronic neglect patients as observed in location-cueing paradigms can be ameliorated specifically using nicotine. Further hypothesis-driven neuropharmacological approaches may open new therapeutic strategies in the treatment of patients with chronic spatial neglect.

Acknowledgements

We thank all patients for participating in the study. We are grateful to our colleagues from the Cognitive Neurology group for valuable support and discussion. The work was supported by a grant from the Deutsche Forschungsgemeinschaft (KFO-112, TP 8). Moreover, we thank Pharmacia/Pfizer (Helsingborg, Sweden) for providing the placebo chewing gums.

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3. Summary and Conclusion Section

In the following section three major points will be discussed: Conclusions will be drawn on the neural correlates of attentional reorienting (3.1), on the nicotinic modulation of attentional reorienting in healthy subjects (3.2) and in patients with neglect (3.3).

3.1 Neural correlates of visuospatial attentional reorienting (résumé of Vossel et al., 2006 and Vossel et al., submitted)

Isolating brain areas involved in the spatial reorienting of attention is commonly accomplished by contrasting invalidly and validly cued targets in the location-cueing paradigm (Arrington, Carr, Mayer & Rao, 2000; Corbetta, Kincade, Ollinger, McAvoy & Shulman, 2000; Thiel, Zilles & Fink, 2004; Giessing, Thiel, Stephan, Rösler & Fink, 2004; Giessing et al., 2006; Vossel et al., 2006, 2008). Here, both superior parietal cortex activation, activation near the intraparietal sulcus (IPS) and activation of the temporo-parietal junction (TPJ) have been reported (see figure 13 for voxels of peak activation).

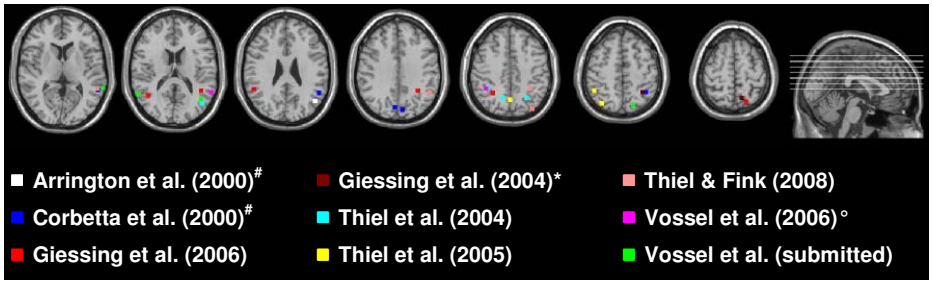

Figure 13. Effect of invalid versus valid spatial cueing on brain activity. Note that for reasons of clarity only activations within parietal and temporo-parietal areas are shown. #The coordinates were transformed from the Talairach and Tournoux (1988) space to the standard coordinate space of the Montreal Neurological Institute (MNI). *Only the results of the event-related analysis are depicted °Results from the pooled analysis over both cue validity conditions (90%, 60%) are reported.

In experiment 1 (1st part) of the present thesis it was observed that right inferior frontal and inferior parietal/temporo-parietal brain regions show stronger activation when attention has to be reoriented in the context of high as compared to low cue validity. In other words, these areas show stronger activation when invalid trials are more infrequent and unexpected and consequently produce larger RT costs. However, the question whether this effect is indeed caused by more demanding attentional reorienting as predicted by attentional gradient models (Madden, 1992) or just by the unexpectedness or saliency of these trials per se cannot be answered by this study. Thus, it was tested in experiment 2 (Vossel et al., submitted) whether infrequently occurring non-spatial visual distractors (colour and orientation changes of the target) evoke similar RT costs and brain responses as invalidly cued targets. Employing such a combination of a location-cueing and a modified oddball paradigm, it was shown that the deviant relative to the standard targets did not produce congruent activation patterns when compared to the activation revealed by the contrast of invalidly and validly cued targets. Even though, the RT costs (deviant – standard targets vs. invalid – valid trials) were almost equally high. Thus, both unexpected location and feature changes disrupted the ongoing cognitive process and produced a slowing of RTs. In the brain, however, the two forms of distraction were represented differently. In particular, activation of the right superior parietal cortex and the right and left TPJ was exclusively observed when contrasting invalid and valid trials and not in the comparison of deviant and standard targets. Common activation was instead observed within an area near the right IPS.

To statistically compare the findings of the two experiments (Vossel et al., 2006 and Vossel et al., submitted), the data of experiment 1 (1st part) were reanalyzed in SPM5 using the procedures described in Vossel et al. (submitted). This was done to rule out that differences between the two studies are caused by the use of different versions of the SPM software or by differences in the preprocessing or estimation steps of the data. The contrast images of each trial type vs. baseline were entered into an ANOVA model in SPM5 with the factors group (study 1, study 2) and experimental condition (validly and invalidly cued targets in the context of 90 and 60% cue validity;

validly and invalidly cued standard and deviant targets). A conjunction analysis testing the conjunction null hypothesis (Friston et al., 2005) was performed on the contrasts capturing reorienting-related activity (invalid > valid trials) in study 1 and 2. This analysis yielded an activation in the right TPJ (x =60, y=-50, z=11, Z=3.43; 9 voxels; p<.001 uncorrected; see figure 12). Interestingly, the reorienting-related activation in this region was stronger in the 90% than in the 60% cue validity condition in study 1, while no differences between reorienting in standard and deviant trials were observed in study 2 (see figure 14).

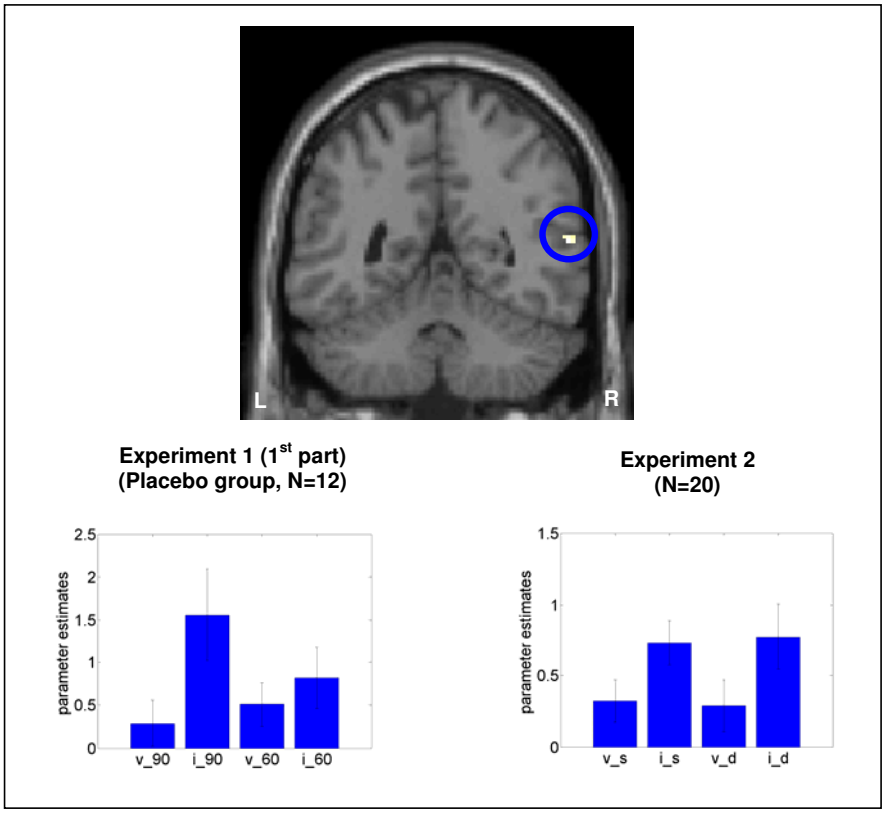

Figure 14. Results of the conjunction analysis of reorienting-related neural activity as observed in study 1 (placebo group) and study 2. Results are shown at p<.001 uncorrected. *v_90*: valid trials in the context of 90% cue validity; *i_90*: invalid trials in the context of 90% cue validity; *v_60*: valid trials in the context of 60% cue validity; *i_60*: invalid trials in the context of 60% cue validity; *v_s*: validly cued standard targets; *i_s*: invalidly cued standard targets; *v_d*: validly cued deviant targets; *i_d*: invalidly cued deviant targets.

Furthermore, it was tested with region of interest (ROI) analyses whether those areas that have been observed to be susceptible to cue validity in study 1 also showed more activation in response to invalidly than to validly cued targets or to deviant as compared to standard targets in study 2. In particular, the contrast of study 1 ([invalidly cued targets 90% cue validity > validly cued targets 90% cue validity] > [invalidly cued targets 60% cue validity > validly cued targets 60% cue validity]) was thresholded at $p<.001$ (uncorr.) and used as a ROI mask for the contrasts [invalid > valid] and [deviants > standards] in study 2. When comparing all invalidly to all validly cued targets in experiment 2, activation within the ROI mask was observed in the right precentral gyrus near the inferior frontal sulcus (x=50, y=10, z=43, Z=3.96; 5 voxels) and in the right TPJ (x=58, y=-52, z=17, Z=3.81; 3 voxels) ($p_{FDR}<.05$). No activation at the applied threshold ($p_{FDR}<.05$) was found within the ROI mask when contrasting deviant to standard targets. Also, no activation was observed when the threshold amounted to $p<.001$ (uncorr.).

In sum, attentional reorienting in the location-cueing paradigm most robustly was accompanied by activation of the right TPJ in the present studies. This is in line with the model of Corbetta and Shulman (2002), in which the right TPJ is supposed to be responsible for directing attention to relevant stimuli that are outside the focus of processing. This function is impaired in patients with spatial neglect and it has been shown that right TPJ is one of the key regions for the manifestation of this neurological syndrome (see figure 9). Moreover, lesions within this area lead to a reorienting-deficit in the location-cueing paradigm (see figure 10; Friedrich et al., 1998). The present data, however, argue against a global function of this region in the detection of unexpected stimuli, as the TPJ activation was not observed in response to infrequent irrelevant feature changes. Instead, it seems to depend on the requirements of the task whether stimulus changes activate the TPJ or not since tasks requiring active detection as well as differential behavioural responses to stimulus changes consistently elicit activation of the TPJ (see figure 4B).

3.2 Behavioural and neural effects of cholinergic stimulation on visuospatial attentional reorienting (Vossel et al., 2008)

One mechanism that has been proposed to underlie the behavioural effect of nicotine in the location-cueing paradigm is a modulation of the use of the top-down information provided by the spatial cues (Yu & Dayan, 2005). Thus, it was tested in experiment 1 whether the effects of nicotine depend on the validity of the spatial cue. In line with the assumption of Yu and Dayan (2005), the first part of experiment 1 (Vossel et al., 2006) has shown that the behavioural effects of a cue validity manipulation under placebo resemble the effects of nicotine since it was found that decreasing cue validity results in lower validity effects. Further supporting Yu and Dayan's model, the 2nd part of experiment 1 (Vossel et al., 2008) revealed that the behavioural effect of nicotine is only observed in the high but not in the low cue validity condition. Moreover, it has been reported in a previous study (Thiel et al., 2005) that only subjects with big validity effects under placebo show a nicotine-induced reduction of the validity effect. Thus, this result was replicated in experiment 1 by using an experimental manipulation of the size of the validity effect.

A neural correlate of a reduced behavioural validity effect in the location-cueing paradigm (i.e., of facilitated attentional reorienting) is a reduction of neural activity in regions of the parietal cortex (Thiel et al., 2005; Giessing et al., 2006; Thiel & Fink, 2008). Experiment 1 extends these findings by showing that this neural effect is modulated by the a priori validity of the spatial cue: Right parietal and frontal brain areas were found to show a nicotine-induced reduction of activity which is stronger in invalid trials in the context of high as compared to low cue validity. Moreover, the result of a reduction of reorienting-related activity under nicotine which was observed in prior studies employing within-subject designs (Thiel et al., 2005; Thiel & Fink, 2008) was replicated using a between-subject design. This is true, however, only for high cue validity conditions (experiment 1: 90%; Thiel et al., 2005 and Thiel & Fink, 2008: 80%). With regard to lower cue validity conditions (~60%) an increase in neural activity was found in invalid trials under nicotine in experiment 1, while a decrease was

observed by Giessing et al. (2006) (see Vossel et al., 2008 for further discussion).

Figure 15 provides an overview over the brain areas that have been reported to show a nicotinic modulation of activity in the location-cueing paradigm in different studies. Apparently, there is variability in the location of the neural effect of nicotine which, however, also applies to the neural correlates of attentional reorienting in general (see figure 13).

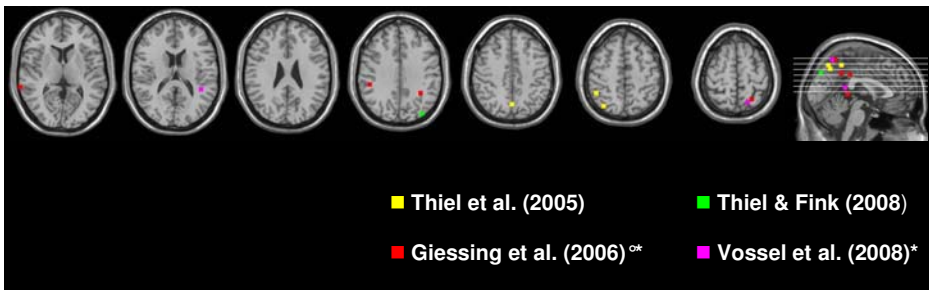

Figure 15. Voxels of peak activation within parietal cortex in 4 studies investigating the effects of nicotine on reorienting-related neural activity in the location-cueing paradigm. Note that for reasons of clarity only activations within parietal and temporo-parietal areas are shown. °Results from the 1 mg as well as the 2 mg nicotine dose are depicted; *Since cue validity affects the behavioural effect of nicotine, the results here depict the interaction of cue validity and nicotine.

The commonality of the results of the depicted studies thus is the nature rather than the exact location of the pharmacological effect in the brain, i.e., the nicotine-induced *reduction* of reorienting-related activity. The variations in the location argue against a direct pharmacological effect of nicotine in the parietal cortex. In line with this argument studies investigating the receptor architecture of the brain have shown that nicotinic receptors are scarcely found in the parietal cortex (see figure 6 and section 1.1.3). Thus, it is more likely that the neural effect of nicotine in the location-cueing paradigm represents an indirect modulation of task-related activity which originates from remote brain regions with a higher density of nicotinic receptors like, e.g., the thalamus or the basal forebrain (which have been shown, for example, to have the highest levels of

binding with [^{3}H] nicotine; Paterson & Nordberg, 2000). However, none of the present pharmacological fMRI studies on the effect of nicotine in the location-cueing paradigm consistently detected altered activity in the thalamus or the basal forebrain in response to nicotine administration. One reason for a missing effect in the basal forebrain could be the signal drop-out and the susceptibility artefacts that are present in this brain area in fMRI. Probably here, imaging techniques like the positron emission tomography (PET) that allow the investigation of the action of receptor ligands in the living brain could provide valuable insights into the direct cortical effects of nicotine in attention tasks (see also Leslie & James (2000) for a review over different imaging techniques for the study of pharmacological effects).

What could be the overall function of the cholinergic system in visuospatial attention? It has been suggested that the cholinergic system is involved in both top-down as well as signal-driven modulation of stimulus detection (Sarter et al., 2005, see also 1.1.3) as well as in balancing these two processing modes (Yu & Dayan, 2005). The results just described can be interpreted within this context as well: In conditions in which there is a strong top-down bias on attentional orienting increasing brain levels of acetylcholine by nicotinic stimulation boosts the influence of signal-driven orienting. Consequently, attentional resources are not so tightly bound to the cued location and behaviourally relevant stimuli occurring outside of the attentional focus can capture attention more easily and are detected more quickly. Consequently, less brain activity is then needed for attentional reorienting.

3.3 Effects of cholinergic stimulation on visuospatial attentional reorienting in patients with spatial neglect

Since it has been proposed that the spatial neglect syndrome results from an attentional bias towards the ipsilesional side of space (i.e., ipsilesional hyperattention) (Gainotti et al., 1991) and from a deficit in attentional reorienting from ipsi- to contralesional space (Posner et al., 1984), it was tested in study 3 whether the cholinergic agonist nicotine could facilitate reorienting of attention and thus target detection of contralesional stimuli in neglect patients. Here, the investigated patient group showed great variability with regard to lesion location as well as neuropsychological and behavioural performance in the location-cueing paradigm under placebo. This reflects the known heterogeneity and composite nature of the spatial neglect syndrome since it has been shown that damage to many different brain areas can result in neglect symptoms and dissociations are often observed between different neuropsychological tests.

Heterogeneous results were also observed concerning the pharmacological effect on attentional reorienting in the present study. The variable that differentiated the responding and non-responding patient group was the location of the lesion in the right parietal cortex. This is in accord with pharmacological imaging studies showing that the nicotinic reduction of the behavioural validity effect is accompanied by modulated neural activity in parietal brain regions (see figure 15). However, it remains unclear, which region exactly is responsible for mediating the pharmacological effect. A recent study by Giessing et al. (2007) investigated the interindividual differences in the nicotinic effect in healthy subjects and tried to reveal neural activation patterns under placebo that could predict the behavioural effect under nicotine in the location-cueing paradigm by means of a partial least squares analysis. This study showed that neural reorienting-related activity under placebo in the left posterior cingulate cortex, the right superior parietal cortex, the right dorsal medial prefrontal cortex, and the left ventral medial prefrontal cortex significantly contributed to that prediction. Although the right superior parietal cortex was a region that was damaged in the non-responding but not in the responding patients, no consistent pattern was observed with regard to the other brain

areas of the network identified in the study of Giessing et al. (2007). However, Giessing et al. (2007) assumed that these areas are more involved in the focusing of attention during valid trials while the superior parietal cortex is related to attentional reorienting. Thus, the superior parietal cortex represents the least common denominator in pharmacological fMRI studies as well as in the present patient study on the effect of nicotine in the location-cueing paradigm.

Taken together, study 3 showed that a cholinergic stimulation can improve the reorienting deficit in the location-cueing paradigm in a subgroup of neglect patients. It also demonstrated, however, that the heterogeneity which characterizes the neglect syndrome per se is also observed in the effects of a pharmacological modulation. This variability is reported in almost every treatment study in neglect patients (for a review, see, e.g. Luauté et al., 2006) and suggests that research on a specific neglect intervention needs to be restricted to patients with circumscribed symptoms and lesion sites. Moreover, more research is needed to reveal valid predictors for the effects of a specific treatment. With regard to pharmacological interventions the present thesis showed that pharmacological fMRI studies in healthy subjects can provide valuable knowledge about the brain tissue that is needed for a specific modulatory effect.

3.4 Future prospects

The present studies have demonstrated how human attentional functions and their neural correlates can be modulated by cognitive as well as by pharmacological factors. The main part of the work was conducted in healthy subjects and thus pertains to the field of basic research. It was shown that attentional reorienting can be influenced by a cholinergic stimulant. However, in prior studies, these effects have not consistently been observed in healthy non-smoking subjects. Future research should, therefore, focus on explaining the variability in this pharmacological effect, for example by investigating the influence of different genotypes. Indeed, it has been shown that gene expression can per se have an impact on the behavioural performance in attention tasks (see, e.g., Greenwood & Parasuraman, 2003). Thus, future studies could address the influence of gene effects on brain activity and on the pharmacological modulation.

The last study of the present thesis attempted to transfer the knowledge from basic research to a clinical setting. Here, more hypothesis-driven studies are needed to develop new therapeutic strategies for patients with spatial neglect. With regard to the effects of cholinergic agonists, studies in larger sample sizes are needed to make valid population-based inferences. Moreover, it needs to be investigated whether pharmacological interventions in neglect patients could already be beneficial at the acute stage of the syndrome to support neuroplasticity and functional reorganisation after brain damage. Here, studies employing between-subject designs in large samples are necessary to control for the spontaneous recovery of neglect patients.

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5. Curriculum Vitae

Name: Simone Vossel

Address: Pfalzgrafenstr. 74, 52072 Aachen, Germany

Nationality: German

Date of birth: April 16th 1980 (Mainz, Germany)

Jan. 2005 – present:	Graduate research assistant and PhD student at the Institute of Neuroscience & Biophysics – Medicine of the Research Centre Jülich and the Institute of Biology & Environmental Sciences of the Carl von Ossietzky University
Oct. 1999 – Nov. 2004:	Study of psychology at the Johannes Gutenberg University in Mainz Diploma in Psychology (mark 1.0 'high distinction')
1990-1999:	'Gymnasium zum Kurfürstlichen Schloss' in Mainz (grammar school with a German-English bilingual wing) A-levels ('Abitur') (average mark 1.4)
1986-1990:	Primary school Mainz-Laubenheim

Name:	Simone Vossel
Anschrift:	Pfalzgrafenstr. 74, 52072 Aachen
Staatsangehörigkeit:	deutsch
Geburtsdatum:	16. April 1980 (Mainz)

Jan. 2005 – heute:	Doktorandin am Institut für Neurowissenschaften & Biophysik – Medizin am Forschungszentrum Jülich und am Institut für Biologie & Umweltwissenschaften der Carl von Ossietzky Universität Oldenburg
Oct. 1999 – Nov. 2004:	Studium der Psychologie an der Johannes Gutenberg Universität zu Mainz Diplom in Psychologie (Note 1.0 ‘mit Auszeichnung’)
1990-1999:	Gymnasium zum Kurfürstlichen Schloss in Mainz (Deutsch-Englisch bilingualer Zug) Abitur (Durchschnittsnote 1.4)
1986-1990:	Grundschule Mainz-Laubenheim

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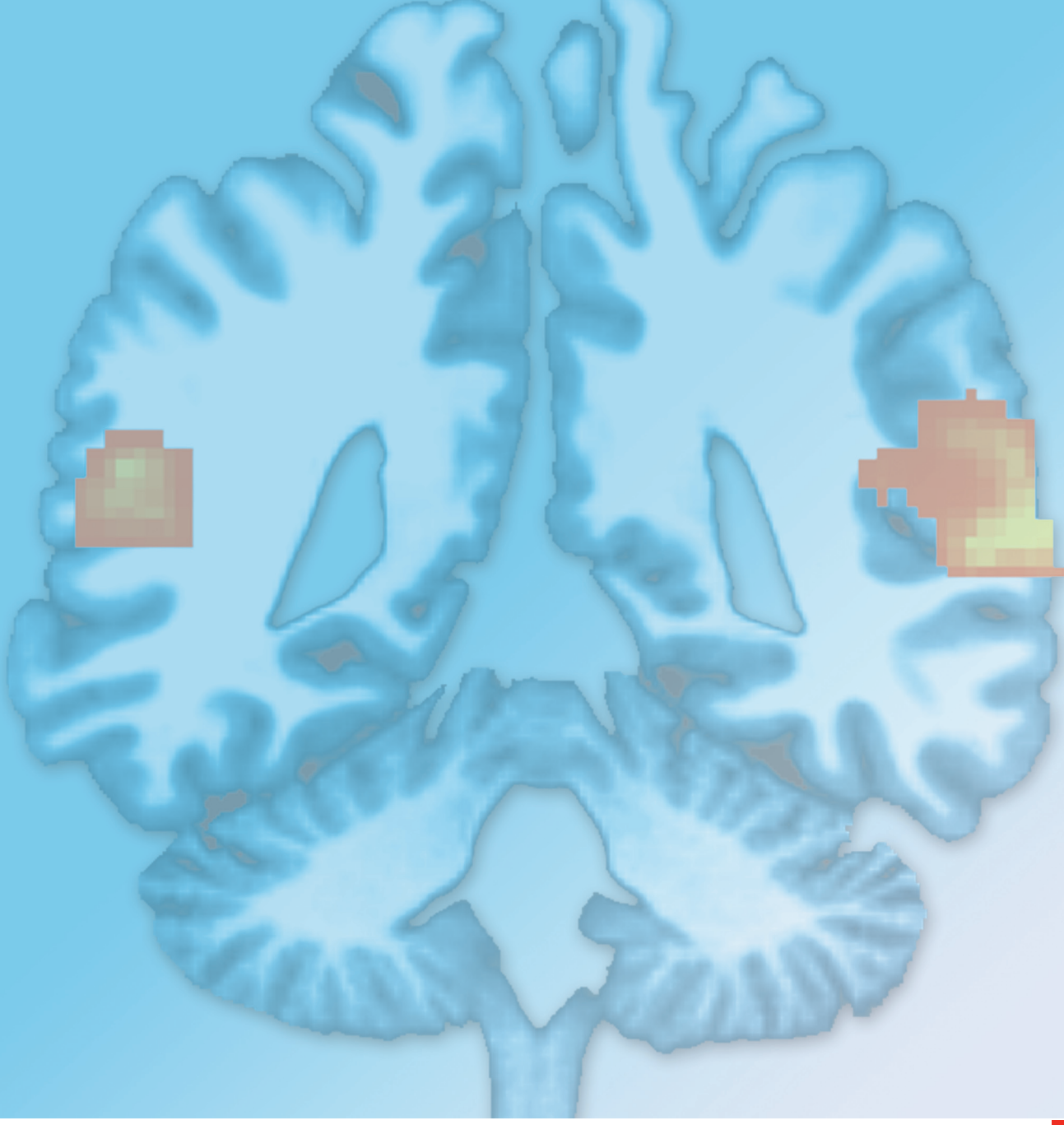

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